Kwon 10/088,884

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This file contains CAS Registry Numbers for easy and accurate
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=> d que 124
L2       103206 SEA FILE=REGISTRY PHOSPHONIC ACID?/CN
L3         3479 SEA FILE=REGISTRY L2 AND POLYMER
L4        99727 SEA FILE=REGISTRY L2 NOT L3
L5        13397 SEA FILE=REGISTRY L4 AND ENE
L6         1252 SEA FILE=REGISTRY L5 AND CYCLO?
L7          362 SEA FILE=REGISTRY L5 AND AZA?
L8         4341 SEA FILE=REGISTRY L5 AND AMIN?
L9          587 SEA FILE=REGISTRY L5 AND PYRIDIN?
L10          99 SEA FILE=REGISTRY L5 AND DODECAN?
L11        5501 SEA FILE=REGISTRY (L6 OR L7 OR L8 OR L9 OR L10)
L12        7467 SEA FILE=HCAPLUS L11
L13         189 SEA FILE=HCAPLUS L12 AND BONE#(3A)LOSS
L14          69 SEA FILE=HCAPLUS L12 AND BONE#(3A)DENSITY
L15         238 SEA FILE=HCAPLUS (L13 OR L14)
L16      509292 SEA FILE=HCAPLUS "THERAPEUTIC USE"/RL
L17         193 SEA FILE=HCAPLUS L16 AND L15
L18         154 SEA FILE=HCAPLUS L17 AND (MAMMAL? OR HUMAN? OR PATIENT? OR
                MOUSE? OR MICE? OR RAT# OR PRIMATE#)
L19          90 SEA FILE=HCAPLUS L18 AND ?PHOSPHON?
L20         228 SEA FILE=HCAPLUS L15 AND (THERAP? OR ADMINIST? OR TREAT? OR
                PHARMACEUT?)
L21         184 SEA FILE=HCAPLUS L20 AND (MAMMAL? OR HUMAN? OR PATIENT? OR
                MOUSE? OR MICE? OR RAT# OR PRIMATE#)
L22         113 SEA FILE=HCAPLUS L21 AND ?PHOSPHON?
L23         118 SEA FILE=HCAPLUS L19 OR L22
L24          59 SEA FILE=HCAPLUS L23 NOT PY>1999


=> d ibib abs 124 1-59

L24  ANSWER 1 OF 59  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2000:54818  HCAPLUS
DOCUMENT NUMBER:          132:203321
TITLE:                    The new selective estrogen receptor modulator MDL
```

Search completed by David Schreiber 308-4292

Kwon 10/088,884

103,323 increases **bone** mineral **density** and **bone** strength in adult ovariectomized **rats**

AUTHOR(S): Ammann, P.; Bourrin, S.; Bonjour, J.-P.; Brunner, F.; Meyer, J.-M.; Rizzoli, R.

CORPORATE SOURCE: Division of Bone Diseases, WHO Collaborating Center for Osteoporosis and Bone Diseases, Department of Internal Medicine, University Hospital, Geneva, CH-1211/14, Switz.

SOURCE: Osteoporosis International (1999), 10(5), 369-376
CODEN: OSINEP; ISSN: 0937-941X

PUBLISHER: Springer-Verlag London Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Selective estrogen receptor modulators (SERMs) can prevent the **bone loss** induced by ovariectomy (OVX), but it is not established whether they can increase bone mass and strength in a curative protocol in ovariectomized osteopenic animals. The authors investigated the influence of a SERM of the new generation, MDL 103,323, on areal bone mineral d. (BMD), as measured by dual-energy x-ray absorptiometry, bone strength and remodeling in OVX osteopenic **rats**. Nine weeks after OVX, 8-mo-old **rats** were divided into six groups of 10 animals. MDL 103,323 was given by gavage at doses of 0.01, 0.1 or 0.6 mg/kg body wt., 5 days a week. The effect of MDL 103,323 was compared with that of the **bisphosphonate** pamidronate (APD), which was injected s.c. at a dose of 1.6 .mu.mol/kg body wt. for 5 days every 4 wk. Lumbar spine (LS), femoral neck (FN), proximal tibia (PT) and midshaft tibia (MT) BMD, bone strength, and proximal tibia histomorphometry, serum osteocalcin, urinary total deoxypyridinoline and serum insulin-like growth factor I (IGF-I) were measured. After 16 wk of **treatment**, BMD changes were -11.4, +4.0, and +6.4%, resp., in OVX controls, in **rats treated** with 0.1 mg/kg MDL 103,323, and in APD-**treated rats** at the level of LS; -0.4, +6.7, and +7.2%, resp., at the level of FN; and -2.6, +5.8, and +6.9%, resp., at the level of PT. MDL 103,323-**treated** animals had a higher trabecular bone vol., a higher no. of trabeculae and smaller intertrabecular spaces compared with OVX controls. Vertebral body ultimate strength was 186, 292, and 249 N in OVX controls, MDL 103,323-**treated rats** and APD-**treated rats**, resp. The **administration** of 0.6 mg/kg of MDL 103,323 did not further increase BMD or bone strength, indicating a bell-shaped dose-response curve. MDL 103,323 lowered plasma osteocalcin concn. and urinary deoxypyridinoline excretion. In **rats treated** with 0.1 mg/kg MDL 103,323, plasma IGF-I was increased as compared with OVX controls (664 ng/mL vs. 527 ng/mL). In conclusion, these results indicate that this new SERM pos. influences BMD and lumbar spine bone strength in estrogen-deficient **rats**.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 2 OF 59 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:818931 HCAPLUS

DOCUMENT NUMBER: 132:54885

TITLE: Anhydrous alendronate monosodium salt formulations

INVENTOR(S): Brenner, Gerald S.; Ostovic, Drazen; Oberholtzer, Earl R., Jr.; Thies, J. Eric

PATENT ASSIGNEE(S): Merck and Co., Inc., USA

SOURCE: U.S., 3 pp.
CODEN: USXXAM

Search completed by David Schreiber 308-4292

Kwon 10/088,884

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6008207	A	19991228	US 1998-133200	19980813
PRIORITY APPLN. INFO.:			US 1998-133200	19980813

AB Disclosed is a method for **treating** and preventing **bone loss** in **patients** by **administering** a formulation of anhyd. alendronate sodium. Also described is a **pharmaceutical** dosage form of anhyd. alendronate sodium, being anhyd. 4-amino-1-hydroxy-butylidene-1,1-**bisphosphonic** acid monosodium salt, in a **pharmaceutically** acceptable excipient.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 3 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:780225 HCAPLUS
DOCUMENT NUMBER: 132:382
TITLE: Risedronate **therapy** prevents corticosteroid-induced **bone loss**: A twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study
AUTHOR(S): Cohen, Stanley; Levy, Robert M.; Keller, Michael; Boling, Eugene; Emkey, Ronald D.; Greenwald, Maria; Zizic, Thomas M.; Wallach, Stanley; Sewell, Kathryn L.; Lukert, Barbara P.; Axelrod, Douglas W.; Chines, Arkadi A.
CORPORATE SOURCE: Metroplex Clinical Research, Dallas, TX, 75235, USA
SOURCE: Arthritis & Rheumatism (1999), 42(11), 2309-2318
CODEN: ARHEAW; ISSN: 0004-3591
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Risedronate, a new pyridinyl **bisphosphonate**, is a potent antiresorptive bone agent. This study examines the safety and efficacy of daily, oral risedronate **therapy** for the prevention of corticosteroid-induced **bone loss**. This multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted in 224 men and women who were initiating long-term corticosteroid **treatment**. **Patients** received either risedronate (2.5 mg or 5 mg) or placebo daily for 12 mo. Each **patient** also received 500 mg of elemental calcium daily. The primary outcome measure was the percentage of change in lumbar spine bone mineral d. (BMD). Secondary measures included proximal femur BMD and incidence of vertebral fractures. After 12 mo, the lumbar spine BMD (mean .+-. SEM) did not change significantly compared with baseline in the 5-mg (0.6 .+-. 0.5%) or the 2.5-mg (-0.1 .+-. 0.7%) risedronate groups, while it decreased in the placebo group (-2.8 .+-. 0.5%; $P < 0.05$). The mean differences in BMD between the 5-mg risedronate and the placebo groups were 3.8 .+-. 0.8% at the lumbar spine ($P < 0.001$), 4.1 .+-. 1.0% at the femoral neck ($P < 0.001$), and 4.6 .+-. 0.8% at the femoral trochanter ($P < 0.001$). A trend toward a decrease in the incidence of vertebral fracture was obsd. in the 5-mg risedronate group compared with the placebo group (5.7% vs. 17.3%; $P = 0.072$). Risedronate was well tolerated, and the incidence of upper gastrointestinal adverse events was comparable among the 3 groups. Risedronate **therapy** prevents **bone**

Search completed by David Schreiber 308-4292

loss in **patients** initiating long-term corticosteroid **treatment**.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 4 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:584626 HCAPLUS
DOCUMENT NUMBER: 131:209069
TITLE: Changes in calcium homeostasis in **patients** undergoing liver transplantation: effects of a single infusion of pamidronate **administered** pre-operatively
AUTHOR(S): Bishop, N. J.; Ninkovic, M.; Alexander, G. J. M.; Holmes, S. D.; Milligan, T.; Price, C.; Compston, J. E.
CORPORATE SOURCE: Addenbrooke's Hospital, University of Cambridge Department of Medicine, Cambridge, CB2 2QQ, UK
SOURCE: Clinical Science (1999), 97(2), 157-163
CODEN: CSCIAE; ISSN: 0143-5221
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Bone** turnover, **bone loss** and fracture risk increase after liver transplantation. It has been postulated that peri-operative **administration** of a **bisphosphonate** might prevent **bone loss** and reduce fracture **rate**. We studied the effects of a single pre-operative dose of pamidronate on biochem. parameters of skeletal metab. in the first month after liver transplantation. In a randomized, single-blind study, six of 12 **patients** with chronic liver disease received 60 mg of pamidronate i.v. on a single occasion 1-30 days before transplantation. Six other **patients** undergoing transplantation received no pamidronate. We measured serum calcium, phosphate, albumin, bone-specific alk. phosphatase, plasma parathyroid hormone and tartrate-resistant acid phosphatase before pamidronate infusion and at frequent intervals during the first 30 post-operative days. In **treated patients**, plasma parathyroid hormone increased 12-fold over baseline values and remained elevated in comparison with baseline at days 26-30; serum calcium and phosphate fell significantly, returning to normal at around day 14 post-operatively. There were no significant changes in any parameter in the untreated group. No changes in bone formation or resorption markers were obsd. in either group. The large increase in plasma parathyroid hormone concns. in the **treated** group is probably secondary to the fall in serum calcium. The magnitude of the increase is much greater than that seen after pamidronate infusion in other **patient** groups. The lack of change in, or correlation of, serum calcium and plasma parathyroid hormone in the untreated group suggests that addnl. factors release calcium from bone after liver transplantation, presumably by increasing bone resorption.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:520030 HCAPLUS
DOCUMENT NUMBER: 131:281508
TITLE: Measurement of **Bone** Mineral **Density** by Dual X-ray Absorptiometry in Paget's Disease Before and After Pamidronate **Treatment**
AUTHOR(S): Laroche, M.; Delpech, B.; Bernard, J.; Constantin, A.;

Mazieres, B.
CORPORATE SOURCE: Service de Rhumatologie, CHU Rangueil, Toulouse, F-31403, Fr.
SOURCE: Calcified Tissue International (1999), 65(3), 188-191
CODEN: CTINDZ; ISSN: 0171-967X
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Third-generation **bisphosphonates** are now currently used in the **treatment** of Paget's disease of bone. Dual X-ray absorptiometry may make it possible to quantify the action of these **bisphosphonates** on bone mineral d. (BMD) in pagetic and nonpagetic bone. We used Lunar DPX L device, a total-body software program (automatic anal. and/or manual windows according to the site and bilateral or unilateral pagetic involvement) to study BMD in 28 **patients** (18 men, 10 women, mean age 69.8 yr) with Paget's disease before and 6 mo after infusions of 60 mg (alk. phosphatase <350 IU) or 120 mg (ALP >350 IU) of pamidronate. Before **treatment**, in the 28 **patients**, the BMD of trabecular pagetic bone was 25% higher than that of nonpagetic bone; in cortical pagetic bone the BMD was 35% higher. After **treatment**, the BMD of trabecular pagetic bone increased by only 1.17%. The BMD of cortical pagetic bone increased by 1.37% whereas nonpagetic cortical bone lost 0.84%, independently of the levels of parathyroid hormone or the **administration** of calcium and vitamin D.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 6 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:319616 HCAPLUS
DOCUMENT NUMBER: 130:347392
TITLE: A meta-analysis on the use of **bisphosphonates** in corticosteroid induced osteoporosis
AUTHOR(S): Homik, Joanne E.; Cranney, Ann; Shea, Beverly; Tugwell, Peter; Wells, George; Adachi, Jonathan D.; Suarez-Almazor, Maria E.
CORPORATE SOURCE: Heritage Medical Research Center, University of Alberta, Edmonton, AB, T6G 2S2, Can.
SOURCE: Journal of Rheumatology (1999), 26(5), 1148-1157
CODEN: JRHUA9; ISSN: 0315-162X
PUBLISHER: Journal of Rheumatology Publishing Co. Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English.

AB Objective. To conduct a meta-anal. on the use of **bisphosphonates** in corticosteroid induced osteoporosis. Methods. A Cochrane systematic review including electronic database searching (MEDLINE and EMBASE), and selected hand searching of ref. lists and scientific abstrs. was conducted. Metaanal. using random and fixed effects modeling was used on the selected trials to calc. summary effect measures. All controlled clin. trials dealing with prevention or **treatment** of corticosteroid induced osteoporosis with **bisphosphonates** of any type and reporting the outcome of interest were assessed. Trials had to involve adults only, and subjects had to be taking a mean steroid dose of 7.5 mg/day or more. Outcomes of interest were change in bone mineral d. (BMD) at the lumbar spine and femoral neck at 6 and 12 mo. If present, data on no. of new fractures and adverse effects were also extd. The extn. was performed by 2 independent reviewers. Results. Results are reported as a weighted mean difference in the percentage change in BMD between the **treatment** and placebo groups, with trials being

weighted by the inverse of their variance. At the lumbar spine the weighted mean difference between the **treatment** and placebo groups was 4.0% (95% CI 2.5, 5.5). At the femoral neck the weighted mean difference was 2.1% (95% CI 0.2, 4.0). Although there was a 24% redn. in spinal fractures, this result did not reach statistical significance. Conclusion. **Bisphosphonates** are effective at preventing and **treating** corticosteroid induced **bone loss** at the lumbar spine. Efficacy regarding fracture prevention cannot be concluded from this anal., although bone d. changes are correlated with fracture risk. **Bisphosphonates** are less efficacious at preventing or **treating** corticosteroid induced osteoporosis at the femoral neck.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 7 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:130217 HCAPLUS
DOCUMENT NUMBER: 130:321073
TITLE: Effects of single and concurrent intermittent **administration** of **human** PTH (1-34) and incadronate on cancellous and cortical bone of femoral neck in ovariectomized **rats**
AUTHOR(S): Zhang, Liu; Endo, Naoto; Yamamoto, Noriaki; Tanizawa, Tatsuhiko; Takahashi, Hideaki E.
CORPORATE SOURCE: Department of Orthopedic Surgery, Niigata University School of Medicine, Niigata, 951-8510, Japan
SOURCE: Tohoku Journal of Experimental Medicine (1998), 186(2), 131-141
CODEN: TJEMAO; ISSN: 0040-8727
PUBLISHER: Tohoku University Medical Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study is to det. the efficacy of concurrent **treatment** with **human** parathyroid hormone, hPTH (1-34), and **bisphosphonate** (incadronate) in augmenting cortical and cancellous bone mass of femoral neck in ovariectomized (OVX) **rats**. Forty-eight 11-wk-old female Sprague-Dawley **rats** were divided into eight groups (six animals in each group). The baseline control group was killed at the beginning of the expt., at 11 wk of age. An ovariectomy was performed in thirty **rats** and twelve **rats** were subjected to a sham surgery. OVX **rats** were untreated for the first four weeks of postsurgery to allow for the development of moderate osteopenia. These animals were then subjected to various **treatments** with either PTH, incadronate, or PTH+ incadronate for a period of 4 wk. Right proximal femora (femoral necks) were used for bone histomorphometry. After OVX 8 wk, there was a significant decrease in cancellous bone mass and cortical bone area of femoral neck in the OVX **rats** when compared to the sham control **rats**. In OVX **rats treated** with PTH alone or PTH+incadronate were completely restored lost cancellous and cortical bone mass of femoral neck by increase bone formation. The bone formation parameters (OS/BS, MS/BS) and bone turnover (BFR/BV) seen with PTH plus incadronate were similar to those seen with PTH **treatment** alone. This indicates that incadronate did not blunt the anabolic action of PTH when used concurrently. The authors' results suggest the following: the femoral neck of OVX **rats** is a suitable sample site for preclin. studies of the prevention of **bone loss** induced by estrogen depletion; concurrent use of incadronate did not blunt the anabolic effect of PTH; concurrent **treatment** showed the best results in

restoring cancellous and cortical bone mass; and it had addnl. benefits for bone strength independent of that achieved by the increase in bone mass.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 8 OF 59 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:103054 HCAPLUS
DOCUMENT NUMBER: 130:119570
TITLE: Prevention of appendicular **bone loss** in Paget's disease following **treatment** with intravenous pamidronate disodium
AUTHOR(S): Stewart, G. O.; Gutteridge, D. H.; Price, R. I.; Ward, L.; Retallack, R. W.; Prince, R. L.; Stuckey, B. G. A.; Kent, G. N.; Bhagat, C. I.; Dhaliwal, S. S.
CORPORATE SOURCE: Department of Diabetes and Endocrinology, Fremantle Hospital and Health Services, Fremantle, 6959, Australia
SOURCE: Bone (New York) (1999), 24(2), 139-144
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It has been shown previously that i.v. pamidronate **treatment** for severe Paget's disease is assocd. with appendicular **bone loss**. This 2 yr study was designed to det. whether cotreatment with calcitriol and a calcium supplement would prevent this. I.v. pamidronate was used to **treat** 49 **patients** with symptomatic Paget's disease. **Patients** were stratified into two groups of differing biochem. severity based on hydroxyproline excretion (HypE) expressed as micromoles per L of glomerular filtrate (GF): (1) a severe group with HypE > 10 .mu.mol/L GF; and (2) a moderate group with HypE 5-10 .mu.mol/L GF. Within each group, **patients** were randomly allocated to receive supplements of calcium and calcitriol (supplemented) or no supplements (unsupplemented) after initiation of pamidronate **therapy**. The severe group received 360 mg of pamidronate as six doses of 60 mg once weekly and the moderate group received 240 mg as four weekly doses of 60 mg. **Patients** were followed for 24 mo following **treatment** and had serial bone densitometry of the forearm measured as well as urine and plasma biochem. When the groups were combined, the unsupplemented **patients** showed a decrease in bone mineral d. (BMD) at the ultradistal forearm site, which persisted to 24 mo. Those supplemented with calcium and calcitriol showed an increase in BMD and the difference between the two groups was significant at all times posttreatment ($p < 0.03$). When the groups were analyzed sep., those with moderate disease again showed significant differences in BMD between supplemented and unsupplemented **patients** at all timepoints. In the severe group, the differences did not reach statistical significance due to smaller **patient** nos. Similar changes in BMD were also obsd. at the forearm shaft site. When serial parathyroid hormone (PTH) levels (with the moderate and severe groups combined) were plotted against time since **treatment** the rise in PTH in the supplemented **patients** was less than the rise in the unsupplemented **patients** ($p < 0.04$). These results suggest that forearm **bone loss** after i.v. pamidronate **treatment** for moderate-to-severe Paget's disease can largely be prevented by **administration** of calcium and calcitriol. The mechanism may be a blunting of the secondary hyperparathyroidism that occurs after i.v. pamidronate. These findings may have wider application

in moderate-to-severe Paget's disease **treated** with other **bisphosphonates**.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 9 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:760916 HCAPLUS
DOCUMENT NUMBER: 130:191838
TITLE: Preadministration of incadronate disodium can prevent **bone loss** in **rat** proximal tibial metaphysis when induced by hindlimb immobilization by bandage
AUTHOR(S): Li, J.; Mashiba, T.; Kaji, Y.; Taki, M.; Komatsubara, S.; Kawanishi, J.; Norimatsu, H.
CORPORATE SOURCE: Department of Orthopedic Surgery, Kagawa Medical University, Kagawa, 761-0793, Japan
SOURCE: Bone (New York) (1998), 23(5), 459-463
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study is to det. whether short-term preadministration of **biphosphonates** prevents **bone loss** in **rat** proximal tibial metaphysis when induced by hindlimb immobilization by bandage. Six-month-old female Sprague Dawley **rats** were injected with incadronate disodium (YM-175, 10 .mu.g/kg) or vehicle, three times per wk for 2 wk (YM or V groups). Then, the left hindlimb was fixed to the abdomen with a bandage (V-B, YM-B groups), or only the abdomen was bandaged as control (V-SHM, YM-SHM groups), for 4 wk. The animals were subsequently killed and left proximal tibiae were processed undecalcified for quant. histomorphometric evaluation. Immobilization-induced cancellous **bone loss** resulted not only from increased percent eroded surface area but also from decreased percent labeling surface and bone formation **rate** in V-B compared with V-SHM animals. In contrast, preadministration of YM-175 decreased percent eroded surface significantly and prevented the **loss** of cancellous **bone** mass in YM-B compared with V-B animals. Cancellous bone mass was neither increased nor decreased by preadministration of YM-175 in YM-SHM animals. Our results suggest that preadministration of **biphosphonates** is effective in prevention of **bone loss** at the tibial metaphysis when induced by hindlimb immobilization in **rats**.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 10 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:723278 HCAPLUS
DOCUMENT NUMBER: 130:276782
TITLE: Effects of **human** PTH(1-34) and **bisphosphonate** on the osteopenic **rat** model
AUTHOR(S): Tanizawa, Tatsuhiko; Yamamoto, Noriaki; Takano, Yuichi; Mashiba, Tasuku; Zhang, Liu; Nishida, Saburo; Endo, Naoto; Takahashi, Hideaki E.; Fujimoto, Ryuhei; Hori, Masayuki
CORPORATE SOURCE: Dep. Orthopedic Surgery, Niigata Univ. Sch. Med., Niigata City, 951-8520, Japan
SOURCE: Toxicology Letters (1998), 102-103, 399-403
CODEN: TOLED5; ISSN: 0378-4274

PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 22 refs. It has been demonstrated that the intermittent **administration** of **human** parathyroid hormone (hPTH) is beneficial for restoration of bone mass in osteoporotic **patients**. The mechanisms of anabolic effects of hPTH have been detd. by ovariectomized **rat** models and other larger remodeling animals. However, **treatment** with hPTH may increase the cancellous bone mass at the expense of cortical bone mass and cessation of the **treatment** results in rapid **bone loss**. Efforts have been made to maintain newly formed bone mass after withdrawal of the hPTH **treatment**. These issues are not well understood. In this article, the authors would like to represent previous studies of their own and others concerning these issues.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 11 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:500479 HCAPLUS
DOCUMENT NUMBER: 129:269762
TITLE: Risedronate
AUTHOR(S): Goa, Karen L.; Balfour, Julia A.
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs & Aging (1998), 13(1), 83-91
CODEN: DRAGE6; ISSN: 1170-229X
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 36 refs. Risedronate is a pyridinyl **bisphosphonate** that can be **administered** orally in lower dosages than other antiresorptive **bisphosphonates**. Like others of its class, risedronate inhibits osteoclast-mediated bone resorption. In exptl. models of osteoporosis, risedronate inhibited **bone loss** and improved trabecular architecture. In **patients** with Paget's disease, pain diminished or disappeared and serum alk. phosphatase levels decreased after **treatment** with oral risedronate at 30 mg/day for .ltoreq.3 mo. Risedronate at 30 mg/day orally for 2 mo significantly reduced pain, whereas etidronate at 400 mg/day orally for 6 mo tended to reduce pain, in a randomized double-blind trial of **patients** with Paget's disease. Oral risedronate at 5 mg/day for .ltoreq.2 yr increased bone mass in postmenopausal women with low or normal bone mass. Risedronate at 2.5 mg/day prevented **bone loss** in postmenopausal women **treated** with glucocorticoids for rheumatoid arthritis. The incidence of gastrointestinal or other adverse events was similar in **patients treated** with risedronate or placebo in clin. trials.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 12 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:440084 HCAPLUS
DOCUMENT NUMBER: 129:118094
TITLE: Randomized trial of pamidronate in **patients** with thyroid cancer: **bone density** is not reduced by suppressive doses of thyroxine, but is increased by cyclic intravenous pamidronate
AUTHOR(S): Rosen, Harold N.; Moses, Alan C.; Garber, Jeffrey; Ross, Douglas S.; Lee, Stephanie L.; Ferguson, Lauren;

Chen, Vicki; Lee, Kevin; Greenspan, Susan L.
CORPORATE SOURCE: Department of Medicine, Division of Gerontology, Charles A. Dana Research Institute and the Harvard-Thorndike Laboratory of the Beth Israel Deaconess Medical Center, Boston, MA, 02215, USA
SOURCE: Journal of Clinical Endocrinology and Metabolism (1998), 83(7), 2324-2330
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Patients** taking suppressive doses of thyroxine (T4) are thought to have accelerated **bone loss** and increased risk of osteoporosis. Therefore, **patients** taking suppressive doses of T4 were randomized to **treatment** with pamidronate (APD) at 30 mg i.v. every 3 mo for 2 yr (APD/T4) or placebo (placebo/T4). **Patients** had measurements of bone mineral d. (BMD) of the spine, hip, radius, and total body every 6 mo for 2 yr. There was no significant **bone loss** at any site in the placebo/T4 group. Ninety-five percent confidence intervals excluded a **rate** of **bone loss** >0.89%/yr for the spine and >0.31%/yr at the total hip. When men were excluded from the anal., there still was no significant **bone loss** for the placebo/T4 group, and confidence intervals did not change. The APD/T4 group showed increases in spine (4.3%), total hip (1.4%), and trochanteric (3.0%) BMDs. In conclusion, premenopausal women and men on suppressive **therapy** with T4 do not lose bone rapidly, and are not at increased risk of developing osteoporosis. A regimen of 30 mg APD given i.v. every 3 mo for 2 yr causes significant suppression of bone resorption and increases in BMD, and may be an acceptable alternative **treatment** for osteoporosis in **patients** who cannot tolerate oral **bisphosphonates**.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 13 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:402319 HCAPLUS
DOCUMENT NUMBER: 129:86015
TITLE: Methods and compositions for preventing and **treating bone loss**
INVENTOR(S): Fuh, Vivian L.; Kaufman, Keith D.; Waldstreicher, Joanne
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Fuh, Vivian L.; Kaufman, Keith D.; Waldstreicher, Joanne
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9825623	A1	19980618	WO 1997-US22344	19971205

W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,

GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9855943	A1	19980703	AU 1998-55943		19971205
PRIORITY APPLN. INFO.:			US 1996-32635P	P	19961209
			GB 1997-221	A	19970108
			US 1997-47174P	P	19970520
			WO 1997-US22344	W	19971205

AB The present invention provides for a method of inhibiting **bone loss** in a subject in need of such **treatment** comprising **administration** of a **therapeutically** effective amt. of the 5.alpha.-reductase type 2 inhibitor finasteride to the subject. The present invention further provides for a method for **treating** and preventing osteoporosis and osteopenia and other diseases where inhibiting **bone loss** may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, comprising **administration** of **therapeutically** effective amt. of the 5.alpha.-reductase type 2 inhibitor finasteride to the subject. Further, the present invention provides for compns. useful in the methods of the present invention, as well as a method of manuf. of a medicament useful for inhibiting **bone loss** and **treating** or preventing osteoporosis and osteopenia. The effect of finasteride on bone mineral d. in men was studied and formulations contg. finasteride were given. Bone anabolic agents, bone antiresorptive agents, estrogens, or antiestrogens may be added to the compns.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 14 OF 59 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:207476 HCAPLUS

DOCUMENT NUMBER: 129:19587

TITLE: Osteotropic drug delivery system (ODDS) based on **bisphosphonic** prodrug. Part 4. Effects of osteotropic estradiol on **bone** mineral **density** and uterine weight in ovariectomized **rats**

AUTHOR(S): Fujisaki, Jiro; Tokunaga, Yuji; Takahashi, Toshiya; Shimojo, Fumio; Kimura, Sumihisa; Hata, Takehisa

CORPORATE SOURCE: Pharmaceutical Pharmakokinetic Research Laboratories, Fujisawa Pharmaceutical Company Ltd., Osaka, 532, Japan

SOURCE: Journal of Drug Targeting (1998), 5(2), 129-138
CODEN: JDTAEH; ISSN: 1061-186X

PUBLISHER: Harwood Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB An osteotropic drug delivery system (ODDS) based on the **bisphosphonic** prodrug was designed for 17.beta.-estradiol (E2) in order to improve **patient** compliance in estrogen replacement **therapy** of postmenopausal osteoporosis. The **bisphosphonic** prodrug of E2, disodium [17.beta.-(3'-hydroxy-1',3',5'-estratrienyloxy)carbonylpropylcarboxamidomethylene]**bisphosphonate** (E2-BP) was synthesized and its effects on bone mineral d. and uterine wt. were investigated in ovariectomized (OVX) **rats**. E2-BP was injected i.v. once a week (4 injections/expt.), and E2 was **administrated** orally 5 times a week (20 **administrations** /expt.). Once a week **treatment** with 0.1 mg/kg E2-BP significantly restored bone mineral redn. by 61.8% without significantly increasing uterine wt. Similarly, once in 4 wk **treatment** with

1.0 mg/kg E2-BP (1 injection/expt.) showed almost the same **therapeutic** effects. On the other hand, 5 times a week oral **treatment** with 1.0 mg/kg E2 significantly improved bone mineral d. by 90.5%, but increased uterine wt. up to 98.2% of that of the sham group. In vitro bone resorption anal. revealed that E2-BP exhibits antiresorptive activity not as a **bisphosphonate** but as a prodrug of E2. These results demonstrated that E2-BP has the potential to improve **patient** compliance in estrogen **therapy** by its minimal adverse effects and less frequent medication.

L24 ANSWER 15 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:111676 HCAPLUS
DOCUMENT NUMBER: 128:226510
TITLE: Maintenance of **bone** mineral **density** of femoral cortex in ovariectomized **rats** after withdrawal of concurrent **administration** of **human** parathyroid hormone (1-34) and incadronate disodium (YM175)
AUTHOR(S): Zhang, Liu; Takahashi, Hideaki E.; Tanizawa, Tatsuhiko; Endo, Naoto; Yamamoto, Noriaki
CORPORATE SOURCE: Department of Orthopedic Surgery, Niigata University School of Medicine, Niigata, 951, Japan
SOURCE: Journal of Bone and Mineral Metabolism (1997), 15(4), 206-212
CODEN: JBMME4; ISSN: 0914-8779
PUBLISHER: Springer-Verlag Tokyo
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study was to evaluate the potential use of a combination of **human** parathyroid hormone (1-34) [hPTH(1-34)] and **bisphosphonate** (incadronate disodium **cycloheptylaminomethylenedisphosphonate** monohydrate, YM175) as a **therapy** for osteoporosis. The authors examd. the effects of concurrent **administration** of PTH and YM175 or single **administration** and the persistence of their **therapeutic** effect after withdrawal on bone mineral d. (BMD) of the femur in ovariectomized **rats** with established osteopenia. One hundred and two 11-wk-old Sprague-Dawley **rats** were divided into sham operation and ovariectomy (OVX) groups. OVX **rats** were untreated for the first 4 wk post ovariectomy to allow for the development of moderate osteopenia. These animals were then subjected to various **treatment** regimens with either PTH, YM175, or both for 4 wk. The animals were then killed at 4 or 12 wk, after withdrawal of the **treatment** and the bone mineral d. (BMD) of distal, middle, proximal part, and total area of the femur were detd. by dual-energy x-ray absorptiometry (DXA). In the distal femur (cancellous bone-rich region), **treatment** with YM175 failed to restore BMD in OVX **rats**, while **treatment** with PTH alone or PTH + YM175 reversed BMD in OVX **rats** after 4 wk of **treatments**. The restored distal BMD by PTH or PTH + YM175 **treatments** could be maintained thereafter until 12 wk withdrawal. In midshaft of the femur (cortical bone-rich region), **treatment** with PTH, YM175, and PTH + YM175 all could increase BMD after 4 wk of **treatments** in the OVX **rats**, but only concurrent **treatment** with PTH + YM175 maintained the BMD of femoral midshaft for 12 wk after withdrawal of the **treatment**. These results suggest that (1) concurrent **treatment** with PTH and YM175 could result in a bone gain not only in cancellous bone but also in cortical bone of the femur, and (2) the restored BMD could be maintained for 12 wk after cessation of the

treatment in cortical bone only by concurrent use of PTH + YM175 in immature ovariectomized **rats**.

L24 ANSWER 16 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:87914 HCAPLUS
DOCUMENT NUMBER: 128:110827
TITLE: Effects of the **bisphosphonate** zoledronate on **bone loss** in the ovariectomized and in the adjuvant arthritic **rat**
AUTHOR(S): Mueller, Klaus; Wiesenberg, Irmgard; Jaeggi, Knut; Green, Jonathan R.
CORPORATE SOURCE: Research Dep., Novartis Pharma A.-G., Basel, CH-4002, Switz.
SOURCE: Arzneimittel-Forschung (1998), 48(1), 81-86
CODEN: ARZNAD; ISSN: 0004-4172
PUBLISHER: Editio Cantor Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of the **bisphosphonate** zoledronate (CAS 118072-93-8, CGP 42446) on trabecular bone in two **rat** models of osteopenia, i.e. the ovariectomized **rat** and the adjuvant arthritic **rat**, was tested and compared to the activity of alendronate and pamidronate. All three **bisphosphonates** prevented **bone loss** in the distal femur and in the lumbar vertebrae in both animal models, as measured by chem. anal. and/or bone densitometry. Zoledronate was the most potent **bisphosphonate**, 10-30 times more potent than alendronate and 120 times more potent than pamidronate.

L24 ANSWER 17 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:766844 HCAPLUS
DOCUMENT NUMBER: 128:43282
TITLE: The role of **bisphosphonates** in the **treatment** of osteoporosis
AUTHOR(S): Reginster, Jean-Yves L.; Halkin, Veronique; Gosset, Christiane; Deroisy, Rita
CORPORATE SOURCE: Bone and Cartilage Metabolism Unit, Department of Epidemiology and Public Health, University of Liege, Liege, Belg.
SOURCE: Drugs of Today (1997), 33(8), 563-570
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: J. R. Prous, S.A.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 58 refs. **Bisphosphonates**, previously called **diphosphonates**, are potent inhibitors of bone resorption and interfere with several stages of the bone-resorption process. Different mechanisms, acting simultaneously and synergistically, are likely to be involved. Several **bisphosphonates** have been tested in various clin. situations related to an increase in osteoclast resorption. Studies on the effects of clodronate in osteoporosis have been conducted either with too few **patients** or with inadequate methodol. The observation of a significant decrease in the **rate** of vertebral fractures in etidronate-**treated patients** with low spine mineral d. and concomitant >2 fractures suggests a possible role for this **bisphosphonate** in the **treatment** of severe osteoporosis. Alendronate has recently been shown to reduce vertebral and nonvertebral fractures in women with osteoporosis. However, particular recommendations for alendronate intake are required to reduce the risk of gastrointestinal side effects. The development of the oral form of

pamidronate was jeopardized by reports of erosive esophagitis which appears to be a common feature of all **aminobisphosphonates**. Preliminary results of studies on the continuous daily oral intake of ibandronate do not compare favorably with those of other **bisphosphonates** on the market or being developed for osteoporosis. Preliminary results with 5 mg risendronate, given either continuously or intermittently, are promising. Demonstration of the minimal ED of this compd. for **treatment** of postmenopausal osteoporosis will be obtained from long-term clin. trials. Tiludronate was previously shown to prevent early postmenopausal **bone loss**. A large, currently ongoing clin. program is evaluating the effects of this compd. in redn. of fractures.

L24 ANSWER 18 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:734100 HCAPLUS
DOCUMENT NUMBER: 128:43819
TITLE: Prevention of Corticosteroid-Induced Osteoporosis with Alendronate in Sarcoid **Patients**
AUTHOR(S): Gonnelli, S.; Rottoli, P.; Cepollaro, C.; Pondrelli, C.; Cappiello, V.; Vagliasindi, M.; Gennari, C.
CORPORATE SOURCE: Institute of Internal Medicine, University of Siena, Italy
SOURCE: Calcified Tissue International (1997), 61(5), 382-385
CODEN: CTINDZ; ISSN: 0171-967X
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Prolonged corticosteroid **administration**, as often required in the **treatment** of sarcoidosis, increases the risk of osteoporosis and fracture. The aim of the present study was to evaluate the usefulness of alendronate, a third generation **bisphosphonate**, in preventing corticosteroid-induced osteoporosis. Forty-three consecutive, previously untreated, sarcoid **patients** (17 men and 26 premenopausal women) were included in the study: 13 needed no **treatment** and served as controls (Group 1) and 30 needed glucocorticoids (prednisone) and were randomly selected to also receive either placebo (n = 15, Group 2) or alendronate 5 mg/day (n = 15, Group 3). Bone mineral d. (BMD) at the ultradistal radius by dual photon absorptiometry (Osteograph 1000, NIM, Verona, Italy) and biochem. markers of bone turnover were measured at baseline and after 6 and 12 mo of glucocorticoid **therapy**. No significant difference was found between Groups 2 and 3 in the mean cumulative dose of prednisone (4945.+-.1956 mg and 5110.+-.2013 mg, resp.). At the end of the study period, BMD increased by 0.8% in the alendronate-**treated** group; in the placebo-**treated** group, BMD decreased by 4.5%. The difference between groups was significant ($P < 0.01$, ANOVA). A significant decrease in markers of bone formation was found in all **patients treated** with prednisone (Groups 2 and 3), independently of alendronate. Alendronate, however, counteracted the increase in markers of bone resorption induced by glucocorticoid **therapy**. The data suggest that alendronate is effective in preventing glucocorticoid-induced **bone loss** in sarcoid **patients**. Further studies on alendronate use in steroid-induced osteoporosis are needed.

L24 ANSWER 19 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:644086 HCAPLUS
DOCUMENT NUMBER: 127:314773
TITLE: Local delivery of an amino **bisphosphonate** prevents the resorptive phase of alveolar bone

following mucoperiosteal flap surgery in **rats**

AUTHOR(S): Yaffe, A.; Iztkovich, M.; Earon, Y.; Alt, I.; Lilov, R.; Binderman, I.

CORPORATE SOURCE: Dept. Prosthodontics, Univ. Hadassah School Dental Medicine, Jerusalem, Israel

SOURCE: Journal of Periodontology (1997), 68(9), 884-889
CODEN: JOPRAJ; ISSN: 0022-3492

PUBLISHER: American Academy of Periodontology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mucoperiosteal flaps are used to access the bone and root surface in a wide range of periodontal procedures and in implant surgery. The authors have demonstrated that the mucoperiosteal surgical flap of the **rat** mandible produces a transient burst of alveolar bone resorption similar to the clin. observations in **humans**. This resorptive activity, when coupled with local irritation factors, may cause confined alveolar **bone loss**. Recently, the authors have demonstrated that an amino **bisphosphonate**, which is used in preventing systemic bond resorption in osteoporosis and other bone diseases, reduces alveolar bone resorption in the **rat** model when **administered** systemically. In this study, the authors evaluated the effect of local delivery of the amino **bisphosphonate** on bone resorption assocd. with mucoperiosteal flaps. Following mucoperiosteal flap elevation in the premolar and molar region of the **rat** mandible, a surgical pellet soaked with amino **bisphosphonate** was locally applied on the exposed bone surface and covered by flap. The results show that local delivery of amino **bisphosphonate** reduces significantly alveolar bone resorption activated by mucoperiosteal flap surgery. This study suggests that local application of amino **bisphosphonate** can be used as an adjunct in **therapy** for reducing bone resorption following surgery.

L24 ANSWER 20 OF 59 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:464046 HCAPLUS
DOCUMENT NUMBER: 127:130958

TITLE: Inhibition of bone resorption by pamidronate cannot restore normal gain in cortical bone mass and strength in tail-suspended rapidly growing **rats**

AUTHOR(S): Kodama, Yoshiaki; Nakayama, Konosuke; Fuse, Hiroaki; Fukumoto, Seiji; Kawahara, Hajime; Takahashi, Hiroo; Kurokawa, Takahide; Sekiguchi, Chiharu; Nakamura, Toshitaka; Matsumoto, Toshio

CORPORATE SOURCE: Department of Orthopedic Surgery, University of Tokyo School of Medicine, Tokyo, Japan

SOURCE: Journal of Bone and Mineral Research (1997), 12(7), 1058-1067
CODEN: JBMREJ; ISSN: 0884-0431

PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To clarify how the changes in bone formation and resorption affect bone vol. and strength after mech. unloading, the effect of inhibition of bone resorption by a potent **bisphosphonate**, pamidronate, on bone mineral d. (BMD), histol., and strength of hind limb bones was examd. using tail-suspended growing **rats**. Tail suspension for 14 days reduced the gain in the BMD of the femur at both the metaphysis rich in trabecular bone and the diaphysis rich in cortical bone. **Treatment** with pamidronate increased the total BMD as well as that of the metaphysis of the femur but had almost no effect on the BMD of the

diaphysis in both control and tail-suspended **rats**. Histol. examns. revealed that 14-day tail suspension caused a **loss** of secondary cancellous **bone** with a redn. in the trabecular no. and thickness in comparison with control **rats**. In the femoral diaphysis, the diam. and cortical bone thickness increased to a lesser degree in tail-suspended **rats** when compared with **rats** without tail suspension, and a marked redn. in bone formation and the layers of alk. phosphatase-pos. cells was obsd. at the periosteal side. Pamidronate **treatment** increased secondary cancellous bone but could not restore normal growth-induced periosteal bone apposition and bone strength. Because the material strength of the femoral diaphysis at the tissue level was not affected by pamidronate **treatment**, the inability of pamidronate to prevent the redn. in phys. strength of the femoral diaphysis does not appear to be due to a change in the quality of newly formed bone. These results demonstrate that tail suspension reduces the growth-induced periosteal modeling drift and that the antiresorptive agent pamidronate is unable to restore normal periosteal bone apposition.

L24 ANSWER 21 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:349188 HCAPLUS
DOCUMENT NUMBER: 127:45466
TITLE: No loss of biomechanical effects after withdrawal of short-term PTH **treatment** in an aged, osteopenic, ovariectomized **rat** model
AUTHOR(S): Mosekilde, Li.; Thomsen, J. S.; Mcosker, J. E.
CORPORATE SOURCE: Department of Cell Biology, Institute of Anatomy, University of Aarhus, Aarhus, DK-8000, Den.
SOURCE: Bone (New York) (1997), 20(5), 429-437
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of the study was to assess the biomech. effects of short-term PTH **treatment** and withdrawal on bone mass and strength in an aged, osteopenic, ovariectomized (ovx) **rat** model. Addnl., the effect of sequential **therapy** with PTH and the **bisphosphonate**, risedronate, the effect of long-term PTH monotherapy, and the effect of long-term risedronate monotherapy were assessed. 96 4-Mo-old **rats** were randomized into nine groups. Eight groups were ovariectomized and one group was sham operated. 12 Mo after surgery, **treatment** regimens were initiated (0W) and were continued for either 2 wk (2W) or 12 wk (12W). The **treatment** regimens were as follows: (1) baseline ovx (0W); (2) ovx-saline (2W); (3) ovx-PTH 1-34 (2W); (4) intact-saline (12W); (5) ovx-saline (12W); (6) ovx-risedronate (12W); (7) ovx-PTH 1-34 (12W); (8) ovx-PTH 1-34 (2W), followed by pause (10W); and (9) ovx-PTH 1-34 (2W), accompanied by risedronate (12W). The effect of **therapy** (endpoint) was measured at three skeletal sites: vertebral bodies; femoral cortical bone; and femoral necks. The results revealed an anabolic, time-dependent effect of PTH 1-34 at all skeletal sites. No loss of anabolic effect was obsd. 10 wk after discontinuation of 2 wk PTH **treatment** in this **rat** model. Risedronate given in sequential **therapy** with PTH produced no significant effect on biomech. properties at any skeletal sites when compared with 2 wk PTH followed by a 10 wk pause. However, when risedronate was given alone, a pos. effect was seen at the vertebral site after a 12 wk **treatment**. On the basis of this study with short-term PTH **treatment** of aged, osteopenic, ovariectomized **rats**, there seemed to be a significant effect of PTH on the biomech. properties and no loss of effect even 10 wk after PTH withdrawal.

L24 ANSWER 22 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:214315 HCAPLUS
DOCUMENT NUMBER: 126:272315
TITLE: **Bisphosphonate** risedronate prevents **bone loss** in women with artificial menopause due to chemotherapy of breast cancer: a double-blind, placebo-controlled study
AUTHOR(S): Delmas, P.D.; Balena, R.; Confravreux, E.; Hardouin, C.; Hardy, P.; Bremond, A.
CORPORATE SOURCE: INSERM Research Unit 403, Hopital E. Herriot, Lyon, 69437, Fr.
SOURCE: Journal of Clinical Oncology (1997), 15(3), 955-962
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study is to det. the effectiveness and safety of the **bisphosphonate** risedronate in preventing **bone loss** in young women with breast cancer and early menopause induced by chemotherapy who are at major risk for the development of postmenopausal osteoporosis. Fifty-three white women, aged 36 to 55 yr, with breast cancer and artificially induced menopause were stratified according to prior tamoxifen use. Thirty-six **patients** received tamoxifen (20 mg/d). Within each stratum, **patients** were randomly assigned to receive risedronate (n = 27) or placebo (n = 26). **Treatment** consisted of eight cycles oral risedronate 30 mg/d or placebo daily for 2 wk followed by 10 wk of no drug (12 wk per cycle). **Patients** were monitored for a third year without **treatment**. Main outcomes of the study were changes in lumbar spine and proximal femur (femoral neck, trochanter, and Ward's triangle) bone mineral d. (BMD), and biochem. markers of bone turnover. In contrast to a significant decrease of BMD at the lumbar spine and hip in the placebo group, there was an increase in BMD in the risedronate group. On **treatment** withdrawal, **bone loss** ensued, which suggests that **treatment** needs to be continuous to maintain a protective effect on bone mass. At 2 yr, the mean difference (.+-. SEM) between groups was 2.5% .+-. 1.2%, (95% confidence interval [CI], 0.2 to 4.9) at the lumbar spine (P = .041) and 2.6% .+-. 1.1%, (95% CI, 0.3 to 4.8) at the femoral neck (P = .029). Similar results were obsd. at the hip trochanter. Results by stratum indicate a beneficial, although partial, effect of tamoxifen in reducing **bone loss**. Risedronate was well tolerated and showed a good safety profile, with no evidence of lab. abnormalities. Risedronate appears to be a safe **treatment** that prevents both trabecular and cortical **bone loss** in women with menopause induced by chemotherapy for breast cancer.

L24 ANSWER 23 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:213099 HCAPLUS
DOCUMENT NUMBER: 126:258293
TITLE: Alendronate: a review of its pharmacological properties and **therapeutic** efficacy in postmenopausal osteoporosis
AUTHOR(S): Jeal, Wendy; Barradell, Lee B.; Mctavish, Donna
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs (1997), 53(3), 415-434
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis

Search completed by David Schreiber, 308-4292

Kwon 10/088,884

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 70 refs. Alendronate is an **aminobisphosphonate** which appears to attenuate, rather than completely inhibiting bone turnover, by suppressing the activity of osteoclasts. Clin. trials have established that 10 mg/day orally **administered** alendronate is the optimum dosage. Despite its poor bioavailability after oral **administration**, alendronate is highly effective at preventing **bone loss** assocd. with the absence of endogenous estrogen. A sustained increase in bone mass was obsd. during alendronate **therapy** without accelerated loss after withdrawal of the drug. Increased bone mass was assocd. with a redn. in the risk and **rate** of occurrence of vertebral fractures. A recent study demonstrated a 47% redn. in the risk of developing new radiog. vertebral fractures over 3 yr in women with low bone mass and pre-existing vertebral fractures. There have been few direct comparisons in clin. trials. However, when compared with calcium or low dosages of salmon calcitonin (salcatonin) **therapy** in women with postmenopausal osteoporosis, alendronate induced a sustained increase in bone mass during **therapy** that was not seen with the comparator. In clin. trials alendronate was generally well tolerated when taken as recommended. Adverse events tended to be transient and usually assocd. with the upper gastrointestinal tract; the most common events included abdominal pain, nausea, dyspepsia, constipation and diarrhea, which are also common with other **bisphosphonates**. Of potential concern are the small no. of reports of **patients** developing esophageal ulceration; however, this adverse event was attributed to noncompliance with the manufacturer's recommendations for **administration** of the drug. In addn., alendronate has not been assocd. with osteomalacia. Studies are still required to establish the long term efficacy of alendronate, particularly with regard to other available **therapies**. Although estrogen replacement **therapy** is generally considered the **treatment** of choice for the management of postmenopausal osteoporosis, many women are unable or unwilling to receive estrogens on a long term basis. Thus, alendronate, with its demonstrated beneficial effects and its good tolerability profile (when taken as recommended), is a promising alternative **treatment** option for the management of postmenopausal osteoporosis.

L24 ANSWER 24 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:177339 HCAPLUS
DOCUMENT NUMBER: 126:246787
TITLE: Effects of prolonged **bisphosphonate** **therapy** and its discontinuation on **bone** mineral **density** in post-menopausal osteoporosis
AUTHOR(S): Orr-Walker, Brandon; Wattie, Diana J.; Evans, Margaret C.; Reid, Ian R.
CORPORATE SOURCE: Department of Medicine, University of Auckland, Auckland, 92019, N. Z.
SOURCE: Clinical Endocrinology (Oxford) (1997), 46(1), 87-92
CODEN: CLECAP; ISSN: 0300-0664
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **bisphosphonates** have proven efficacy in the management of post-menopausal osteoporosis. However, the benefits of prolonged (> 2 yr) **administration** and the effects of discontinuation of **bisphosphonate treatment** are not clear. We have

Search completed by David Schreiber 308-4292

previously reported a 2-yr, randomized, double-blind, placebo-controlled trial of pamidronate **therapy** (150 mg/day) in women with established post-menopausal osteoporosis. We now report the bone mineral d. (BMD) changes in those women who continued for a third year of active **treatment** and were then obsd. off **therapy** for a further 12 mo. Twenty-two women (mean age 66 yr) continued on pamidronate in year 3, and in 16 of these the effect of subsequent discontinuation of **therapy** for 12 mo were studied. BMD was measured in the total body, lumbar spine and proximal femur using a lunar DPX-L dual-energy, X-ray absorptiometer. The third year of **therapy** with pamidronate was assocd. with a significant further gain in BMD only at the lumbar spine (2.cntdot.1 .+-. 0.cntdot.6%, P = 0.cntdot.003), resulting in a total gain of 9.cntdot.5 .+-. 1.cntdot.0% at that site over 3 yr of **treatment**. In the total body, BMD tended to decline (-0.cntdot.6 .+-. 0.cntdot.3%) in year 3. One year after discontinuation of pamidronate, there were significant losses of BMD in the total body (-1.cntdot.9 .+-. 0.cntdot.3%, P <0.cntdot.0001) and femoral trochanter (-2.cntdot.7 .+-. 0.cntdot.9%, P = 0.cntdot.01), and non-significant changes at the lumbar spine (-0.cntdot.9 .+-. 0.cntdot.8%), femoral neck (-0.cntdot.5 .+-. 1.cntdot.6%), and Ward's triangle (-2.cntdot.9 .+-. 3.cntdot.7%). By the end of one year off **therapy**, BMD was greater than baseline only in the lumbar spine (7.cntdot.1 .+-. 1.cntdot.1%, P<0.cntdot.0001) and femoral trochanter (4.cntdot.5 .+-. 1.cntdot.88%, P<0.cntdot.03). In the total body, BMD was 0.cntdot.3 .+-. 0.cntdot.7% below the values at the trial's inception (P = 0.cntdot.7). These data demonstrate that the **rate** of bone gain assocd. with **bisphosphonate** use slows over time, and that significant **bone loss** follows withdrawal of these agents. These findings have important implications for the duration of use of these novel drugs in the **therapy** of osteoporosis and suggest a need for close observation following their discontinuation.

L24 ANSWER 25 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:105205 HCAPLUS
DOCUMENT NUMBER: 126:122508
TITLE: **Bisphosphonate** cement composition to prevent aseptic loosening of orthopedic implant devices
INVENTOR(S): Simpson, Hamish; Athanasou, Nick; Yates, Ashley J.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA; Simpson, Hamish; Athanasou, Nick; Yates, Ashley J.
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9639107	A1	19961212	WO 1996-US8515	19960603
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN				
RW: KE, LA, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2223450	AA	19961212	CA 1996-2223450	19960603
EP 831756	A1	19980401	EP 1996-917041	19960603
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				

JP 11511041 T2 19990928 JP 1996-501089 19960603
PRIORITY APPLN. INFO.: US 1995-470404 A 19960603
WO 1996-US8515 W 19960603

AB Disclosed is a **bisphosphonate** bone cement for preventing peri-prosthetic **bone loss** and aseptic loosening of a joint prosthesis in **patients**, which cement contains a **bisphosphonate** bone resorption inhibitor, e.g. Na or Ca salt of alendronate and a **pharmaceutically** acceptable polymeric carrier such as poly(Me methacrylate). A compn. contg. Me methacrylate, N,N-dimethyl-p-toluidine, and chlorophyll was added to a compn. contg. Me methacrylate-Me acrylate copolymer, benzoyl peroxide, ZrO2, chlorophyll, and gentamicin, then alendronate Na was added to give a cement mixt.

L24 ANSWER 26 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:101602 HCAPLUS
DOCUMENT NUMBER: 126:99324
TITLE: **Bisphosphonate therapy** for **bone loss** associated with rheumatoid arthritis
INVENTOR(S): Daifotis, Anastasia G.; Yates, Ashley J.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA; Daifotis, Anastasia G.; Yates, Ashley J.
SOURCE: PCT Int. Appl., 9 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9639150	A1	19961212	WO 1996-US8361	19960603
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2221416	AA	19961212	CA 1996-2221416	19960603
AU 9659679	A1	19961224	AU 1996-59679	19960603
AU 703887	B2	19990401		
EP 831843	A1	19980401	EP 1996-916971	19960603
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 11506750	T2	19990615	JP 1996-500987	19960603

PRIORITY APPLN. INFO.: US 1995-471464 19950606
WO 1996-US8361 19960603

AB **Bisphosphonates**, and particularly alendronate (I) , can prevent or **treat bone loss** assocd. with rheumatoid arthritis. Men and women with active rheumatoid arthritis ages 18-80 were given 5-20 mg I/day orally for 1 yr. In addn. to I **therapy**, **patients** were also given 1000 mg calcium and 250 IU vitamin D daily. **Patients** who received daily oral I had increased spine and hip bone mineral d. relative to both their baseline scores and to **patients** receiving placebo.

L24 ANSWER 27 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:82190 HCAPLUS
DOCUMENT NUMBER: 126:181313

Kwon 10/088,884

TITLE: Intravenous injections of ibandronate in the **treatment** of postmenopausal osteoporosis
AUTHOR(S): Thiebaud, D.; Kriegbaum, H.; Huss, H.; Christiansen, C.; Burckhardt, P.
CORPORATE SOURCE: Dep. Med., Univ. Hosp., Lausanne, CH-1011, Switz.
SOURCE: International Congress Series (1996), 1118(Osteoporosis 1996), 321-325
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oral **treatment** of osteoporosis with **bisphosphonates** relies on compliance, the absorption being low and suppressed by simultaneous food intake. I.v. (i.v.) **treatment** with pamidronate (once every 3 mo) revealed to be an effective alternative, but required infusions. The high potency of ibandronate allows i.v. bolus injections. To test the efficacy of this **treatment** in osteoporosis in a double-blind, placebo-controlled study, 126 postmenopausal women (yr) with osteoporosis received placebo or ibandronate (four doses) every 3 mo. All received 1 g calcium/day. Bone mineral d. (BMD, g/cm2) was measured by dual x-ray absorptiometry (DXA; Hol. QDR 1500 or 2000), at the lumbar spine and the hip (femoral neck, trochanter and total hip). Lumbar BMD increased with the two lower doses over 9 mo only, but with the doses of 1 and 2 mg up to 12 mo, with some dose dependency. BMD of the hip increased slightly with some dose-dependency. Placebo (i.e., calcium) produced a decrease in urinary NTX telopeptides and of osteocalcin. Urinary excretion of NTX telopeptides decreased after 1 mo in all ibandronate groups, with clear dose-dependency. The 3-monthly telopeptides remained decreased compared to the controls, except with 0.25-mg ibandronate. Osteocalcin decreased progressively and dose-dependently. Compared to the placebo group, there was only a trend to an increased no. of **patients** with minor adverse events, including acute phase reactions. Probably drug-related side effects were leg cramps in one **patient**, and general pains in another who dropped out. In conclusion, **treatment** of osteoporosis by i.v. bolus injections of the **bisphosphonate** ibandronate was effective in increasing BMD through a dose-dependent inhibition of bone resorption.

L24 ANSWER 28 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:44943 HCAPLUS
DOCUMENT NUMBER: 126:152253
TITLE: Oncologic, endocrine & metabolic Alendronate (Fosamax): clinical utility in metabolic bone disease
AUTHOR(S): Hayes, Joathan; Sambrook, Philip
CORPORATE SOURCE: Garvin Inst. Med. Res., St. Vincent's Hosp, Sydney, Australia
SOURCE: Expert Opinion on Investigational Drugs (1996), 5(12), 1691-1705
CODEN: EOIDER; ISSN: 0967-8298
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 80 refs. Alendronate is a member of the class of drugs known as **bisphosphonates**, potent inhibitors of bone resorption which act via inhibition of osteoclast function. Unlike first generation **bisphosphonates**, alendronate does not appear to have deleterious effects on bond mineralizations at doses which inhibit bone resorption. **Bisphosphonates** have been studied in the management of a broad

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range of skeletal disorders characterized by increased bone turnover, including hypercalcemia of malignancy, metastatic bond disease, primary and secondary hyperparathyroidism, and Paget's disease of bone. More recently, **bisphosphonates** have also been studied in the prevention and **treatment** of established **bone loss** in **patients** with osteoporosis. In this respect, alendronate has recently been shown to increase bone mass in the spine, femoral neck and total body of postmenopausal women with osteoporosis, and to reduce the incidence of vertebral, hip and wrist fractures, the progression of vertebral deformities and height loss in these subjects. The drug appears to be safe and well tolerated apart from a low incidence of chem. esophagitis. Alendronate therefore offers a promising alternative to hormone replacement **therapy** for **treatment** of osteoporosis in postmenopausal women and may also may play a role in the management of other types of osteoporosis.

L24 ANSWER 29 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:563923 HCAPLUS
DOCUMENT NUMBER: 125:238556
TITLE: Clodronate and osteoporosis
AUTHOR(S): Kanis, J. A.; McCloskey, E. V.; Beneton, M. N. C.
CORPORATE SOURCE: WHO Collaborating Centre Metabolic Bone Diseases, University Sheffield, Sheffield, S10 2RX, UK
SOURCE: Maturitas (1996), 23(Suppl.), S81-S86
CODEN: MATUDK; ISSN: 0378-5122
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Bisphosphonates** are widely used in disorders assocd. with increased resorption of bone, particularly in Paget's disease of bone and the hypercalcemia of malignancy. Their undoubted efficacy and relatively low toxicity makes them attractive candidates for the management of osteoporosis. The three **bisphosphonates** widely tested are etidronate, pamidronate and clodronate. Whereas pamidronate can only be given by i.v. infusion, clodronate may be given i.v. or by mouth. Unlike etidronate, even high doses of clodronate do not impair the mineralization of bone, making it suitable for long-term use in osteoporosis. Clodronate has been shown to inhibit exptl. induced increases in bone resorption and in **patients** prevents **bone loss** at the menopause and during immobilization. Short-term and long-term studies indicate that clodronate appears to stop **bone loss** at the lumbar spine in **patients** with vertebral osteoporosis. Long-term studies of the effects at the hip are not yet reported. The effects of clodronate on the frequency of osteoporotic fractures are not yet known and will demand well controlled long-term prospective studies.

L24 ANSWER 30 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:513773 HCAPLUS
DOCUMENT NUMBER: 125:158635
TITLE: Bone mass anabolic composition comprising olpadronate
INVENTOR(S): Papapoulos, Socrates; Ferretti, Jose Luis; Labriola, Rafael; Mondelo, Nelida; Roldan, Emilio J. A.
PATENT ASSIGNEE(S): Gador S.A., Argent.; University of Leiden
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9619998	A1	19960704	WO 1995-EP5142	19951227
W: AU, BR, CA, CN, CZ, FI, JP, KP, KR, NO, PL, RU, SK, US, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2208714	AA	19960704	CA 1995-2208714	19951227
AU 9644347	A1	19960719	AU 1996-44347	19951227
AU 701258	B2	19990121		
EP 800397	A1	19971015	EP 1995-943216	19951227
R: BE, DE, ES, FR, GB, IT, NL				
BR 9510123	A	19971230	BR 1995-10123	19951227
JP 11502506	T2	19990302	JP 1995-520215	19951227
ZA 9510995	A	19970630	ZA 1995-10995	19951228
US 5885973	A	19990323	US 1997-875202	19971010
PRIORITY APPLN. INFO.:			EP 1994-120799 A	19941228
			WO 1995-EP5142 W	19951227

AB Methods are provided for bone mass anabolic preservation or augmentation in **human** or other animal subjects affected by osteoporosis or other metabolic bone disorder characterized by systemic or regional **bone loss**, using **bisphosphonates** formulations, wherein the bone mass anabolic compn. contains effective non-toxic doses of [3-(N,N-dimethylamine)-1-hydroxypropylidene]-**bisphosphonic** acid or olpadronate or the monosodium (I) or other **pharmaceutically** acceptable salt thereof. Thus, 11.11 kg of [3-(N,N-dimethylamine)-1-hydroxypropylidene]-**bisphosphonic** acid (prepn. given) was added to 33.3 L of sodium hydroxide (50.7 g/L) and 122 L of methanol and was dried in an oven with forced air circulation until const. wt. of 10.7 kg I was obtained. Oral **administration** of 5 and 50 mg/day to **patients** between 2-70 yr with vertebral osteoporosis increased bone mass up to 13% of initial values during 3 yr follow-up. In children, not only increases of bone mass were obtained, but there was also radiol. evidence of augmentation of cortical and trabecular bone.

L24 ANSWER 31 OF 59 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1996:472404 HCAPLUS
DOCUMENT NUMBER:	125:185773
TITLE:	Time-dependent changes in biochemical bone markers and serum cholesterol in ovariectomized **rats**: Effects of raloxifene HCl, tamoxifen, estrogen, and alendronate
AUTHOR(S):	Frolik, C. A.; Bryant, H. U.; Black, E. C.; Magee, D. E.; Chandrasekhar, S.
CORPORATE SOURCE:	Endocrine Research, Lilly Research Laboratories, Indianapolis, IN, 46285, USA
SOURCE:	Bone (New York) (1996), 18(6), 621-627 CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER:	Elsevier
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB **Bone loss** assocd. with postmenopausal osteoporosis can be reduced by **treatment** with anti-resorptive agents such as estrogen or **bisphosphonates**. Whereas **bisphosphonates** primarily affect **bone loss**, estrogens have an advantage of also lowering serum cholesterol levels, although they have a detrimental effect in the uterus. Recently, raloxifene HCl, a selective estrogen receptor modulator (SERM), has been shown to decrease both

bone loss and cholesterol levels without the neg. uterine effects. These anti-resorptive agents reduce bone turnover, which can be evaluated by measuring bone turnover markers. To compare the effects of estrogen, 2 SERMs (raloxifene HCl and tamoxifen), and alendronate, a **bisphosphonate** that inhibits **bone loss** by an estrogen-independent pathway, on metabolic bone markers and cholesterol levels, **rats** were ovariectomized 2 wk prior to 3 wk of daily oral **treatment** with raloxifene HCl (3 mg/kg), ethynyl estradiol (0.1 mg/kg), tamoxifen (3 mg/kg), or alendronate (3 mg/kg). Raloxifene HCl, tamoxifen, and ethynyl estradiol reduced serum cholesterol to levels below control values within 4 days after initiation of **treatment**, whereas alendronate had no effect. After 3 wk of **treatment**, serum cholesterol values in ethynyl estradiol **treated** animals, although still below the control value, had risen 6.4-fold; raloxifene HCl and tamoxifen values rose by only 1.4-1.5-fold. Therefore, compared with estrogen, SERMs may have a longer-term suppressive effect on serum cholesterol. At 4 days of **treatment**, ovariectomized **rats** had a 1.4-fold increase in serum osteocalcin level compared with controls. Ethynyl estradiol lowered this level within 1 wk of **treatment** by 18%, with a more pronounced redn. of 34% at 3 wk. In contrast, raloxifene HCl, tamoxifen, or alendronate had very little effect after the 1st week (6 to 13% redn.), although there was an 18 to 25% redn. by 3 wk. Urinary pyridinoline levels, elevated 1.4-fold in the ovariectomized **rat** compared with controls 2 wk after surgery, were reduced to control values after 2 wk of **treatment** with raloxifene HCl, ethynyl estradiol, tamoxifen, or alendronate. These data support the concept that estrogen, raloxifene HCl, tamoxifen, and alendronate inhibit **bone loss** in the ovariectomized animal by reducing bone resorption. The results also indicate that for **treatment** of postmenopausal osteoporosis, raloxifene HCl may have an advantage over the other anti-resorptives studied in having both non-uterotrophic and hypocholesterolemic effects in addn. to its ability to inhibit bone resorption.

L24 ANSWER 32 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:162371 HCAPLUS
DOCUMENT NUMBER: 124:249437
TITLE: Alendronate
AUTHOR(S): Shinkai, Ichiro; Ohta, Yukari
CORPORATE SOURCE: Merck Res. Laboratories, Rahway, NJ, 07065-0900, USA
SOURCE: Bioorganic & Medicinal Chemistry (1996), 4(1), 3-4
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 10 refs. Alendronate (Fosamax) is a potent **aminobisphosphonate** deriv. which has shown efficacy in postmenopausal osteoporosis, Paget's disease, and malignant hypercalcemia. In hyperparathyroid **rats**, alendronic acid reduces **bone loss**, while in ovariectomized **rats**, alendronic acid prevents and reverses estrogen deficiency-induced bone changes. In ovariectomized baboons, alendronic acid decreases the **rate** of bone turnover, while increasing bone strength and vol. In **rats**, alendronic acid is more potent at inhibiting bone resorption than etidronic acid and has a higher safety margin. After sequestration into bone, the half-life is estd. to be more than 10 yr, however, biol. effects diminish post-**treatment**. Unlike earlier **biphosphonate** compds., alendronate contains an amino group side-chain, which imparts

greater potency and specificity. As an inhibitor of bone resorption, alendronate is 200 to 1000 times more potent than etidronate and approx. 100 times as potent as clodronate or tiludronate. Alendronate localizes preferentially at active sites of bone resorption, and bone resorption has been inhibited at doses that have no effect on bone mineralization. Results from two three-year pivotal trials with 994 postmenopausal women with osteoporosis support the conclusion that alendronate builds healthy bone. In **patients treated** with daily alendronate, 10 mg for 3 yr, a progressive increase from baseline in bone mineral d. occurred at the spine (8.2%) and hip (7.2%), compared with **patients treated** with placebo, in whom bone mineral d. decreased between 0.65 and 1.16%. Oral alendronate significantly decreases biochem. markers of bone turnover in post menopausal women to levels similar to those found in healthy premenopausal women. Bone biopsy results indicate that the quality of new bone formed in **treated patients** is normal. In postmenopausal women with osteoporosis, alendronic acid significantly reduces the no. of **patients** with new vertebral fractures by nearly 50%, reduces the no. of vertebral fractures per **patient**, reduces the apparent severity of vertebral fractures, and reduces height loss compared to placebo. Alendronate was licensed to Merck & Co., Inc. by Istituto Gentili SPa of Pisa, Italy in 1988 and is approved in 28 other countries.

L24 ANSWER 33 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:998286 HCAPLUS
DOCUMENT NUMBER: 124:66604
TITLE: **Pharmaceutical** compositions containing platelet-derived growth factor and bone seeking drugs for osteoporosis and bone regeneration
INVENTOR(S): Antoniades, Harry N.; Lynch, Samuel E.; Finkelman, Richard D.
PATENT ASSIGNEE(S): Institute of Molecular Biology, Inc., USA
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9528950	A1	19951102	WO 1995-US5047	19950418
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9522973	A1	19951116	AU 1995-22973	19950418
PRIORITY APPLN. INFO.:			US 1994-230114	19940420
			WO 1995-US5047	19950418

AB **Pharmaceutical** formulations useful for **treating bone loss** consist of a simple mixt. of platelet-derived growth factor (PDGF) and a bone-targeting anionic compd. of at least one neg. charge at pH 6.8. The invention also features a compn. contg. PDGF and an anti-resorptive agent. Alendronate 0.015 g was added to 36.3 mL of 50 mM sodium acetate buffer contg. 11.03 mg/mL PDGF along with 0.10 mL phosphate buffered saline (PBS) and 0.20 mL of 10 M NaOH. To this soln.

were added 3.31 mL PBS and 0.275 mL of 2M tris.HCl and 0.002 mL glacial acetic acid to yield a 40 mL soln. with a final pH of 7.04 to obtain an injection soln. of the invention. Ovariectomized **rats** were injected 3 times/wk with 200.mu.L of the above injection soln. and at 2.5 wk after the start of injection bone measurements were obtained by dual energy X-ray absorptiometry. The bone d. of the **treated** animals was increased over baseline 300.0% more than the corresponding change from baseline in PBS-**treated** animals.

L24 ANSWER 34 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:997354 HCAPLUS
DOCUMENT NUMBER: 124:45749
TITLE: Iontophoretic delivery of **bisphosphonates** to the alveolar bone
INVENTOR(S): Shinoda, Hisashi; Horiuchi, Hiroshi
PATENT ASSIGNEE(S): Procter and Gamble Co., USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9528145	A1	19951026	WO 1995-US3727	19950324
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 09511927	T2	19971202	JP 1995-526974	19950324
US 5668120	A	19970916	US 1995-495266	19950627
PRIORITY APPLN. INFO.:			US 1994-228982	19940418
			WO 1995-US3727	19950324

OTHER SOURCE(S): MARPAT 124:45749
AB The present invention relates to methods of inhibiting alveolar bone resorption or the undesirable movement of teeth of a **human** or other animal comprising (1) **administering** a reservoir to the gingival tissue of the oral cavity such that the reservoir is in contact with the exposed tissue nearest to the alveolar bone to be **treated** wherein the reservoir is a compn. having a pH which maintains an active compd. in a neg. charged state and (2) passing a safe and effective amt. of elec. current through 2 electrodes, one electrode being a neg. electrode in contact with the reservoir and the second electrode being a pos. electrode in contact with the **human** being **treated** . A soln. contg. 50 mM risedronic acid was applied to the gingival margin of a periodontitis **patient** with progressive disease. An iontophoretic current of 0.2 mA was applied for 10 mins and the **treatment** was repeated one wk later. The progression of alveolar bone resorption was arrested for 3 mos as detd. by radiog. evaluation.

L24 ANSWER 35 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:936033 HCAPLUS
DOCUMENT NUMBER: 124:21554
TITLE: The effect of pamidronate in a new model of immobilization in the dog
AUTHOR(S): Grynpas, M. D.; Kasra, M.; Renlund, R.; Pritzker, K. P. H.
CORPORATE SOURCE: Department Pathology, University Toronto, Toronto, ON, Can.
SOURCE: Bone (New York) (1995), 17(4, Suppl., Proceedings of

the International Conference on Animal Models in the Prevention and Treatment of Osteopenia, 1995), 225s-32s
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Bone loss** resulting from immobilization or disuse has been shown in **humans** following paralysis or bedrest. We have developed a new model of immobilization in the dog which is reversible and we have studied the effect of pamidronate (APD) in this model. Twelve mature beagle dogs were fitted with specially designed mesh jackets. These jackets were used to bind the left forelimb against the body of the dog, thereby preventing wt. bearing on that limb. The exptl. group (n=6) was **treated** with an I.V. dose of 0.45 .mu.mol/kg/day APD (pamidronate) for 7 days followed by 3 wk without **treatment**. This cycle was repeated 3 times for a total of 12 wk. The control group (n=6) followed the same pattern, but received only saline injections. At the end of the expt., the dogs were sacrificed and the humeri and radii cleaned of soft tissues. Mineralization profiles, which det. the distribution of mineralization densities of the cortical and trabecular bone were obtained and the main fractions were analyzed chem. Static histomorphometric parameters were detd. on 5 .mu.m undecalcified sections from the distal humerus and on 50 .mu.m section of the humeral shaft. Three point bending and torsional testing were performed on the radius. Immobilization induces hypomineralization in cortical and cancellous bone but is prevented by APD **treatment** in cancellous. Immobilization in this model induces osteopenia and increases turnover in cancellous bone. These effects are counteracted by APD. Finally, cortical bone d. and stiffness are reduced by immobilization but this is prevented by APD **treatment**. This expt. shows that the mature dog model is useful to study the immobilization-induced increase of bone turnover and concomitant decrease in bone d., stiffness and mineralization. It also shows that these effects of immobilization can be prevented by **treatment** with the **bisphosphonate** pamidronate.

L24 ANSWER 36 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:743306 HCAPLUS
DOCUMENT NUMBER: 123:160762
TITLE: Inhibitory effects of a **bisphosphonate** (risedronate) on experimental periodontitis in **rats**
AUTHOR(S): Shoji, K.; Horiuchi, H.; Shinoda, H.
CORPORATE SOURCE: School of Dentistry, Tohoku University, Sendai, 980-77, Japan
SOURCE: Journal of Periodontal Research (1995), 30(4), 277-84
CODEN: JPDRAY; ISSN: 0022-3484
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study was designed to examine whether systemic **administration** of a **bisphosphonate**, risedronate, could prevent alveolar bone resorption in **rats** with exptl. periodontitis. On day 1, an elastic ring was placed around the neck of the right mandibular 1st molar to induce inflammatory periodontitis. The animals were given daily injections of either 0.9% NaCl (control group) or 0.8, 1.6 or 3.2 .mu.moles (s.c.) of risedronate/kg (exptl. groups) from days 1 to 7, and were killed on day 8. Histol. examns. and detn. of bone mineral d. in the interdental area between the 1st and 2nd molars with an

image analyzer revealed that the presence of the elastic ring induced a **loss** of attachment and **bone** resorption in the control group. Vigorous bone resorption, with appearance of a large no. of osteoclasts, was obsd. in the interdental and bifurcation areas. In the exptl. groups, however, the resorption of alveolar **bone** and the **loss** of **bone** mineral content in these areas were prevented in a dose-dependent fashion, esp. at doses of 1.6 and 3.2 .mu.moles/kg. Many osteoclasts were detached from the surface of the alveolar bone and had degenerated appearances, such as rounded shapes, loss of polarity and pyknosis. These results suggest that **administration** of risedronate is effective in preventing bone resorption in periodontitis.

L24 ANSWER 37 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:601357 HCAPLUS
DOCUMENT NUMBER: 123:684
TITLE: Effects of large doses of olpadronate (dimethyl-pamidronate) on mineral density, cross-sectional architecture, and mechanical properties of **rat** femurs
AUTHOR(S): Ferretti, Jose Luis; Mondelo, Nelida; Capozza, Ricardo Francisco; Cointry, Gustavo Roberto; Zanchetta, Jose Ruben; Montuori, Esteban
CORPORATE SOURCE: Centro de Estudios de Metabolismo Fosfocalcico (CEMFoC), Universidad Nacional de Rosario, Rosario, 2000, Argent.
SOURCE: Bone (New York, NY, United States) (1995), 16(4, Suppl.), 285S-293S
CODEN: BONEDL; ISSN: 8756-3282
DOCUMENT TYPE: Journal
LANGUAGE: English
AB As part of a safety-assessment study, doses of 8, 40, and 200 mg/kg per day, 6 days per wk, of sodium olpadronate (dimethyl-APD, Me2-APD) were given by gavage to 10-wk-old male and female **rats** during 27 wk. Only the 200 mg/kg per day dose provoked toxic effects and a meaningful growth depression, regardless of the animal gender. In male animals, doses of 40 or 200 mg/kg per day improved strength, stiffness, and cross-sectional moment of inertia (CSMI) of femur diaphyses despite the toxic effects obsd. at the highest dose. Changes in bone mech. properties were a consequence of those induced in CSMI. Regression analyses showed a **treatment**-induced improvement in bone modeling (as assessed by CSMI) for the same level of bone material stiffness (as expressed by calcd. values of elastic modulus). The high dependency of results on body mass bearing suggested that these effects were exerted through an increase in the efficiency of bone mechanostat. Strikingly, they were not evident in female **rats**. If not related to a lower bone bioavailability of **bisphosphonates** in female **rats** as described by others, this phenomenon may have reflected: (1) their smaller biomass; and/or (2) a less effective mechanostatic regulation of bone architecture derived from a higher bone material stiffness related to male animals. An increase of BMD with a predominance toward the distal region was obsd. in all femurs studied. This effect, unrelated to the obsd. changes in mech. properties, seems to express a lack of remodeling of primary cartilage or bone tissue.

L24 ANSWER 38 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:534868 HCAPLUS
DOCUMENT NUMBER: 122:282512
TITLE: Direct stereological estimation of three-dimensional

connectivity in **rat** vertebrae: effect of estrogen, etidronate and risedronate following ovariectomy

AUTHOR(S): Boyce, R. W.; Wronski, T. J.; Ebert, D. C.; Stevens, M. L.; Paddock, C. L.; Youngs, T. A.; Gundersen, H. J. G.

CORPORATE SOURCE: Procter and Gamble Pharmaceuticals, Norwich, NY, USA

SOURCE: Bone (New York, NY, United States) (1995), 16(2), 209-13
CODEN: BONEDL; ISSN: 8756-3282

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Newly developed unbiased stereol. methods were employed to investigate the effects of estrogen deficiency on the three-dimensional connectivity of vertebral cancellous bone from ovariectomized (OVX) **rats**. The effects of two classes of antiresorptive agents, estrogen and **bisphosphonates**, on changes in connectivity in this animal model were also evaluated. Female **rats** were either sham-operated (sham-op) or surgically OVX at 90 days of age. OVX **rats** were **administered** either vehicle, estrogen (10 .mu.g/kg 17-.beta.-estradiol, 5 days/wk s.c.), etidronate disodium (5 mg/kg s.c.) or risedronate (5 .mu.g/kg s.c.). The **bisphosphonates** were **administered** daily for 1 wk followed by 3 wk with no **treatment**. **Treatment** duration was 360 days. Systematic random sections, 30-.mu.m thick, were prepd. from methyl-methacrylate-embedded decalcified second lumbar vertebrae. Total trabecular no. and connectivity d. were estd. using the ConnEulor principle. Vertebral cancellous bone vol. was estd. on undecalcified sections from the first lumbar vertebrae. Connectivity d. and cancellous bone vol. were significantly reduced (approx. 25% and 40%, resp.) in the OVX group compared with the sham-op group. Estrogen **treatment** essentially maintained connectivity and cancellous bone vol. at the level of the sham-op **rats**. Connectivity d. and total trabecular no. were significantly increased in the etidronate- and risedronate-**treated** **rats** compared with both the sham-op and OVX **rats**. These data demonstrate that redn. in the three-dimensional connectivity of vertebral cancellous bone is a long-term consequence of ovariectomy in the **rat**. This redn. in connectivity can be effectively prevented by the **administration** of antiresorptive agents such as estrogen, etidronate and risedronate. The increase in connectivity in the **bisphosphonate-treated** groups compared with the sham-op group may be a reflection of the combined effects of these agents on resorptive cell recruitment and function in the growing **rat** skeleton. These results suggest that these agents may be clin. useful in preventing resorption-dependent perforation and loss of trabecular elements which may be an important component of estrogen-deficiency-related **bone loss** in women.

L24 ANSWER 39 OF 59 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:596485 HCAPLUS

DOCUMENT NUMBER: 121:196485

TITLE: Subregion analysis of the **rat** femur: a sensitive indicator of changes in **bone density** following **treatment** with thyroid hormone or **bisphosphonates**

AUTHOR(S): Rosen, H. N.; Middlebrooks, V. L.; Sullivan, E. K.; Rosenblatt, M.; Maitland, L. A.; Moses, A. C.; Greenspan, S. L.

CORPORATE SOURCE: Charles A. Dana Res. Inst., Beth Israel Hospital,

Boston, MA, 02215, USA
SOURCE: Calcified Tissue International (1994), 55(3), 173-5
CODEN: CTINDZ; ISSN: 0171-967X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Measurements of bone mineral d. (BMD) by dual x-ray absorptiometry (DXA) is a precise and accurate way to assess changes in BMD due to a variety of causes. However, the degree of **bone loss** may vary depending on the skeletal site examd. The authors postulated that interventions that change bone d. would have a different effect on an area rich in trabecular bone, such as the distal femur, than on other subregions of the femur. Male Sprague-Dawley **rats** (325-350 g) were **treated** with triiodothyronine (T3), a **bisphosphonate** (pamidronate), or placebo for 21 days and then sacrificed. Ex vivo BMD of the proximal, distal, mid and total femur were measured by DXA. The authors found that mean BMD of hyperthyroid **rats** was significantly lower than controls at all femoral subregions. However, the difference in mean BMD between hyperthyroid and control **rats** was greatest at the distal femur (8.6%). In **rats treated** with **bisphosphonate**, mean BMD was significantly higher than controls at the proximal, distal, and total femur. The difference in mean BMD between controls and **rats treated** with **bisphosphonate** was greatest at the distal femur (31.8%). Furthermore, pamidronate-**treated rats** had lower mean mid-femur BMD than controls. The authors conclude that changes in BMD after **treatment** with **bisphosphonate** or T3 are greatest at the distal femur subregion, and that **treatment** with **bisphosphonate** may cause a slight redn. in mid-femur BMD. Future studies examg. changes in BMD in the **rat** femur after interventions that alter mineral metab. should include subregion anal.

L24 ANSWER 40 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:595927 HCAPLUS
DOCUMENT NUMBER: 121:195927
TITLE: Use of **phosphonates** for the **treatment** of osteoporosis
INVENTOR(S): Francis, Marion David; Boyce, Rogely Waite
PATENT ASSIGNEE(S): Procter and Gamble Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9400129	A1	19940106	WO 1993-US5267	19930604
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9344038	A1	19940124	AU 1993-44038	19930604
AU 659329	B2	19950511		
EP 648120	A1	19950419	EP 1993-914339	19930604
EP 648120	B1	19971229		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 07508278	T2	19950914	JP 1994-502366	19930604
HU 70210	A2	19950928	HU 1994-3762	19930604

AT 161423	E	19980115	AT 1993-914339		19930604
ES 2111163	T3	19980301	ES 1993-914339		19930604
CA 2138367	C	19980922	CA 1993-2138367		19930604
NO 9405058	A	19950228	NO 1994-5058		19941228
PRIORITY APPLN. INFO.:			US 1992-906609	A	19920630
			WO 1993-US5267	A	19930604

OTHER SOURCE(S): MARPAT 121:195927

AB A method of increasing bone mass in a **human** or other **mammal** afflicted with osteoporosis comprises 30 days' systemic **treatment** with a high-potency **phosphonate**, e.g. R1C(PO3H2)2(CH2)nXR2 (R1 = H, Cl, NH2, OH; X = NH, O, bond; R2 = 5-7-membered heterocycle; n = 0-7), at 0.00001-0.1 mg P/kg/day, provided that the **phosphonate** is **administered** .gtoreq.1 day of every 30-day **treatment** period, and each 30-day **treatment** period may be followed by a rest period of .gtoreq.1 day. Thus, a 65-yr-old woman with considerable **bone loss** was **treated** with repeated cycles of 2-(3-pyridinyl)-1-**hydroxyethanebisphosphonate** (0.05 mg P/kg/day orally for 14 days) followed by a 7-14-day rest period. After 1 yr, bone mass was increased 7% and mobility was improved.

L24 ANSWER 41 OF 59 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1994:400826 HCAPLUS
DOCUMENT NUMBER:	121:826
TITLE:	The effect of a **bisphosphonate** on bone volume and eggshell structure in the hen
AUTHOR(S):	Thorp, B.H.; Wilson, Sandra; Rennie, Sarah; Solomon, Sally E.
CORPORATE SOURCE:	Inst. Anim. Physiol. Genet., Edinburgh Res. Stn., Roslin/Midlothian, EH25 9PS, UK
SOURCE:	Avian Pathology (1993), 22(4), 671-82 CODEN: AVPADN; ISSN: 0307-9457
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB **Bisphosphonates**, used in the prevention and **treatment** of osteoporosis in man, can prevent **bone loss** in exptl. models of osteoporosis in **mammals**. In egg-laying hens there is a high incidence of bone fractures which are due to osteoporosis. Alendronate, a **bisphosphonate**, was given to three groups of hens in mid-lay. Different doses of alendronate were given to each group and group 4 was a control. The birds were killed after 2 wk of **treatment**. The hens receiving the highest dosage of alendronate (1 mg/kg every 2nd day) ceased laying and had reduced serum calcium concns. Lower dosages of alendronate (0.1 and 0.01 mg/kg every 2nd day) resulted in normal egg prodn. and serum calcium concns. Egg shells with ultra-structural features indicative of reduced shell quality were produced by hens on the two higher dosages, but the egg shells from the controls and from the hens on the lowest dosage were considered normal. When alendronate was **administered** to hens in mid-lay there was no effect on trabecular bone vols., but there was a redn. in mean medullary bone vol. in some groups. In a second expt., pullets were **treated** with alendronate (0.01 mg/kg twice a week) before the onset of lay. The pullets were killed after laying their first egg. In the pullets **treated** with alendronate, this protocol resulted in a significantly greater vol. of trabecular (structural) bone at the onset of lay.

L24 ANSWER 42 OF 59 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:400823 HCAPLUS

Kwon 10/088,884

DOCUMENT NUMBER: 121:823
TITLE: Parenteral pamidronate prevents thyroid hormone-induced **bone loss** in **rats**
AUTHOR(S): Rosen, Harold N.; Sullivan, E. Kelly; Middlebrooks, V. Leah; Zeind, Adib John; Gundberg, Caren; Dresner-Pollak, Rivka; Maitland, Lauri A.; Hock, Janet M.; Moses, Alan C.; Greenspan, Susan L.
CORPORATE SOURCE: Charles A. Dana Res. Inst., Beth Israel Hosp., Boston, MA, USA
SOURCE: Journal of Bone and Mineral Research (1993), 8(10), 1255-61
CODEN: JBMREJ; ISSN: 0884-0431
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Pamidronate (APD) is a **bisphosphonate** that prevents **bone loss** from a variety of causes. The authors studied the role of APD in preventing thyroid hormone-induced **bone loss**. A total of 32 **rats** were assigned to one of four **treatment** groups: (1) -APD/triiodothyronine (-T3), (2) -APD/+T3, (3) +APD/-T3, or (4) +APD/+T3. In the first of two studies, the **rats** received APD for the first week and T3 for the second week, and then their blood was analyzed for alk. phosphatase and osteocalcin. Alk. phosphatase and osteocalcin were significantly higher ($p < 0.05$) in hyperthyroid **rats** (-APD/+T3, 3.9 .+-. 0.25 .mu.kat/L and 23 .+-. 1.6 nM, resp.) than in control animals (2.53 .+-. 0.28 .mu.kat/L and 18.3 .+-. 1.4 nM, resp.). Hyperthyroid **rats** pretreated with APD (+APD/+T3) had levels of alk. phosphatase and osteocalcin no different from controls. In a second study, **rats** were divided into the same four groups, except they received APD/placebo and T3/placebo concomitantly for 3 wk. At the end of the study, bone mineral d. (BMD) of the femur, spine, and whole body was measured by dual-energy x-ray absorptiometry, and the calcium content of the femora was measured directly. In hyperthyroid **rats** (-APD/+T3) BMD was significantly lower than in controls in the spine (0.201 .+-. 0.004 vs. 0.214 .+-. 0.002 g/cm2, $p < 0.05$) and femur (0.204 .+-. 0.003 vs. 0.218 .+-. 0.002, $p < 0.05$). In hyperthyroid **rats** pretreated with APD (+APD/+T3) BMD of the spine, femur, and total body was significantly higher than in controls ($p < 0.001$). Similar differences among groups were seen in femur calcium content. The authors conclude that hyperthyroid **rats** have an increased **rate** of **bone** turnover and **bone loss** that can be prevented by coadministration of a **bisphosphonate**.

L24 ANSWER 43 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:69966 HCAPLUS
DOCUMENT NUMBER: 120:69966
TITLE: The effects of the **aminobisphosphonate** alendronate on thyroid hormone-induced osteopenia in **rats**
AUTHOR(S): Yamamoto, Michiko; Markatos, Angelo; Seedor, J. Gregory; Masarachia, Patricia; Gentile, Michael; Rodan, Gideon A.; Balena, Raffaella
CORPORATE SOURCE: Dep. Bone Biol. Osteoporosis Res., Merck Research Lab., West Point, 19486, USA
SOURCE: Calcified Tissue International (1993), 53(4), 278-282
CODEN: CTINDZ; ISSN: 0171-967X
DOCUMENT TYPE: Journal
LANGUAGE: English

Search completed by David Schreiber. 308-4292

Kwon 10/088,884

AB Hyperthyroidism, either endogenous or iatrogenic, leads to increased bone turnover and osteopenia. This study was conducted to examine whether thyroid hormone excess in **rats** causes bone changes similar to those seen in **patients** with hyperthyroidism, and the effects of the **aminobisphosphonate** alendronate on the thyroid hormone-induced bone changes. Sprague-Dawley male **rats**, divided into four groups, received L-thyroxine (T4) at 250 .mu.g/kg/day (+T4) or vehicle (-T4) s.c. six times per wk and alendronate at 1.75 mg/kg (+ALN) or vehicle (-ALN) orally twice a week. **Rats** were sacrificed after 3 wk of **treatment**, blood samples were analyzed for serum T4, triiodo-L-thyronine (T3), and osteocalcin, and the proximal tibiae were processed for histomorphometric anal. Serum T4 and T3 levels measured 20-24 h after the last injection were 2 to 2.5-fold higher in +T4 groups than in -T4 groups. Serum osteocalcin was higher in +T4/-ALN group than in the other groups, which were not statistically different from each other. T4 **treatment** (+T4/-ALN) decreased the amt. of cancellous bone vol. (-45%) and increased osteoid surface (+254%), osteoblast surface (+111%), and osteoclast surface (+176%) relative to control values. Alendronate increased the bone vol. above control values in both T4-**treated** (+T4/+ALN) and untreated (-T4/+ALN) **rats**, and prevented the T4-induced increase in bone turnover in +T4/+ALN **rats**. It is concluded that excess thyroid hormone induces cancellous **bone loss** assocd. with high **bone** turnover in the **rat**, and this **bone loss** can be prevented by alendronate through the inhibition of osteoclastic activity.

L24 ANSWER 44 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:69830 HCAPLUS
DOCUMENT NUMBER: 120:69830
TITLE: Skeletal effects of withdrawal of estrogen and **diphosphonate treatment** in ovariectomized **rats**
AUTHOR(S): Wronski, T. J.; Dann, L. M.; Qi, H.; Yen, C. F.
CORPORATE SOURCE: Coll. Vet. Med., Univ. Florida, Gainesville, FL, 32610, USA
SOURCE: Calcified Tissue International (1993), 53(3), 210-216
CODEN: CTINDZ; ISSN: 0171-967X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The study was designed to det. the skeletal effects of withdrawal of estrogen and **diphosphonate treatment** in the estrogen-deplete state. Groups of ovariectomized (OVX) **rats** were **treated** with vehicle alone, estrogen, or the **diphosphonates** etidronate or risedronate for a 180-day period. A group of sham-operated control **rats** was **treated** for 180 days with vehicle alone. All **treatments** were then terminated, followed by sequential sacrifice of **rats** at 0, 35, 90, 180, and 360 days after withdrawal of **treatment**. The proximal tibia from each animal was processed undecalcified for quant. bone histomorphometry. At the end of the **treatment** period, vehicle-**treated** OVX **rats** were characterized by cancellous osteopenia and increased bone turnover relative to vehicle-**treated** control **rats**. **Treatment** of OVX **rats** with estrogen or **diphosphonates** depressed bone turnover and protected against cancellous osteopenia. During the withdrawal period, OVX **rats** previously **treated** with estrogen exhibited rapid **bone loss** assocd. with increased **bone** turnover. The bone protective effect of the

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hormone in OVX **rats** was nearly completely lost by 90 days of withdrawal. In contrast, OVX **rats** maintained low levels of bone turnover and normal cancellous bone mass at 180 days of withdrawal from **diphosphonate treatment**. The results suggest that estrogen-deplete women who are withdrawn from estrogen replacement are at high risk for subsequent **bone loss**. They further suggest that widely spaced periods of intermittent **diphosphonate treatment** may be sufficient to prevent the development of osteopenia in postmenopausal and oophorectomized women.

L24 ANSWER 45 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:69559 HCAPLUS
DOCUMENT NUMBER: 120:69559
TITLE: The effects of 2-year **treatment** with the **aminobisphosphonate** alendronate on bone metabolism, bone histomorphometry, and bone strength in ovariectomized nonhuman **primates**
AUTHOR(S): Balena, R.; Toolan, B. C.; Shea, M.; Markatos, A.; Myers, E. R.; Lee, S. C.; Opas, E. E.; Seedor, J. G.; Klein, H.; et al.
CORPORATE SOURCE: Research Lab., West Point, PA, 19486, USA
SOURCE: Journal of Clinical Investigation (1993), 92(6), 2577-86
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study examines the effect of 2 yr of **treatment** with the **aminobisphosphonate** alendronate (ALN) (0.05 or 0.25 mg/kg i.v. ALN every 2 wk) on estrogen deficiency **bone loss** and **bone** strength changes in ovariectomized (OVX) baboons (n = 7 per group) and the ALN mode of action at the tissue level. Biochem. markers of bone turnover increased in OVX animals and were maintained by ALN **treatment** at non-OVX levels (low dose) or below (high dose). **Treatment** for 2 yr produced no cumulative effects on bone turnover markers. Histomorphometry showed a marked increase in cancellous bone remodeling in OVX animals. Activation frequency increased from 0.48 to 0.86 per yr (L5 vertebra), and the osteoid surfaces from 9 to 13.5%. No changes were obsd. in eroded and osteoclast surfaces. ALN **treatment** decreased activation frequency and indexes of bone formation to control levels (low dose) or below (high dose), did not change indexes of mineralization, and increased bone mineral d. (BMD) in the lumbar vertebrae (L2-L4) by 15% at 0.25 mg/kg relative to vehicle-**treated** animals. The mean strength of cancellous bone (L4) increased by 44% (low ALN dose) and 100% (high dose), compared with vehicle. The strength of individual bones correlated with the square of the L2-L4 BMD (r = 0.91). In conclusion, ALN **treatment** reversed the effects of ovariectomy on cancellous bone turnover and increased bone mass and bone strength in baboons.

L24 ANSWER 46 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:46639 HCAPLUS
DOCUMENT NUMBER: 120:46639
TITLE: IGF-I and pamidronate increase **bone** mineral **density** in ovariectomized adult **rats**
AUTHOR(S): Ammann, Patrick; Rizzoli, Rene; Muller, Klaus; Slosman, Daniel; Bonjour, Jean Philippe
CORPORATE SOURCE: Div. Clin. Pathophysiol., World Health Organ. Collaborating Cent. Osteoporosis and Bone Dis., Switz.
SOURCE: American Journal of Physiology (1993), 265(5, Pt. 1),

E770-E776
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Effects induced by insulin-like growth factor I (IGF-I) and/or the **bisphosphonate** pamidronate (APD) on bone mineral d. (BMD) of the lumbar spine and proximal and midshaft tibia were studied in adult **rats** made osteopenic by ovariectomy, using dual-energy x-ray absorptiometry. IGF-I, which was **administered** by osmotic minipumps implanted s.c. for 6 wk, caused a dose-dependent increase of BMD at the three investigated sites. A 4-wk course of IGF-I, followed by intermittent cyclical APD **administration**, induced significant increases of BMD at the levels of spine and proximal tibia. At midshaft tibia, where cortical bone predominates, BMD was increased by IGF-I only. In conclusion, IGF-I increased BMD at sites with trabecular and/or cortical bone, whereas the APD influence was mainly detectable in the former site only.

L24 ANSWER 47 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:23521 HCAPLUS
DOCUMENT NUMBER: 120:23521
TITLE: Effects of aminohydroxybutane **bisphosphonate** on bone growth when **administered** after hind-limb **bone loss** in tail-suspended **rats**
AUTHOR(S): Apseloff, Glen; Girten, Beverly; Weisbrode, Steven E.; Walker, Monica; Stern, Lawrence S.; Krecic, Mary Ellen; Gerber, Nicholas
CORPORATE SOURCE: Coll. Med., Ohio State Univ., Columbus, OH, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1993), 267(1), 515-21
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of aminohydroxybutane **bisphosphonate** (AHBuBP) on bone after disuse osteopenia were studied in tail-suspended **rats**. Male Sprague-Dawley **rats** (wt. range, 313-352 g) randomized into four groups of eight animals received 2 mL kg-1 day-1 of either AHBuBP (0.3 mg kg-1 day-1) or normal saline (vehicle) s.c. on days 14 and 15 of a 28-day expt. The groups were nonsuspended, saline; suspended on days 14 to 28, saline; suspended on days 0 to 28, AHBuBP; and suspended on days 0 to 28, saline. On days 19 and 26, all **rats** received 15 mg/kg (1 mL/kg) of calcein. On day 28, they were sacrificed and their tibias and femurs were analyzed in vitro for bone d., strength and stiffness. The tibias were also analyzed histomorphometrically. The tibias and femurs from AHBuBP-**treated rats** were as dense as those in the nonsuspended group, whereas tail suspension in the untreated **rats** for 14 and 28 days caused a significant decrease in bone d. However, in measurements of bone strength and stiffness, the samples from the **rats** that received AHBuBP were similar to those of untreated **rats** suspended for 14 days, suggesting the newly formed bone was weaker. In the AHBuBP group, compared with all others, static histol. measurements of the proximal tibial metaphyses showed an increased bone area and perimeter and a decreased percentage of osteoid perimeter without a difference in the percentage of eroded perimeter. Dynamic histol. studies showed a decreased bone formation **rate** and decreased longitudinal growth **rate**. The retention of the first label was greatest in this group, which indicated a marked decrease in bone resorption. Although AHBuBP reduced normal bone formation, the

net bone mass increased because of the greater inhibition of resorption, which resulted in bone with inferior mech. strength.

L24 ANSWER 48 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:641322 HCAPLUS
DOCUMENT NUMBER: 119:241322
TITLE: The **aminobisphosphonate** alendronate inhibits **bone loss** induced by thyroid hormone in the **rat**: comparison between effects on tibiae and vertebrae
AUTHOR(S): Balena, R.; Markatos, A.; Gentile, M.; Masarachia, P.; Seedor, J. G.; Rodan, G. A.; Yamamoto, M.
CORPORATE SOURCE: Dep. Bone Biol. Osteoporosis Res., Merck Res. Lab., West Point, PA, 19486, USA
SOURCE: Bone (New York, NY, United States) (1993), 14(3), 499-504
CODEN: BONEDL; ISSN: 8756-3282
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aims of this study were to develop a **rat** model of hyperthyroidism and to det. the efficacy of alendronate in the prevention of thyroid hormone-induced **bone loss**. Ten week-old Sprague-Dawley **rats** injected with thyroxine 250 .mu.g/kg/day (+T4) or vehicle (-T4) were **treated** with alendronate (+ALN) or vehicle (-ALN) orally 0.5 mg/kg/day. After 3 wk of **treatment** histomorphometric parameters of cancellous bone remodeling were assessed in the proximal tibia and in the first lumbar vertebra. In the secondary spongiosa of the tibia T4 **treatment** caused significant **bone loss**, assocd. with increased **bone** turnover; trabecular bone vol., trabecular thickness and trabecular no. were significantly decreased. Osteoid and osteoclast surfaces increased in +T4/-ALN as compared to control. Alendronate prevented the increase in bone turnover and increased bone vol. above control values without interfering with the recruitment of osteoclasts. These changes were not apparent in the vertebra. It is concluded that excess thyroid hormone in the **rat** induces high turnover **bone loss** in the tibia which can be prevented by alendronate through an inhibition of osteoclastic activity. The lack of effects of thyroid hormone on the vertebra may be ascribed to a lower **rate** of basal bone turnover at that site.

L24 ANSWER 49 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:205205 HCAPLUS
DOCUMENT NUMBER: 118:205205
TITLE: Aminohydroxybutane **bisphosphonate** and clenbuterol prevent bone changes and retard muscle atrophy respectively in tail-suspended **rats**
AUTHOR(S): Apseloff, Glen; Girten, Beverly; Walker, Monica; Shepard, Dale R.; Krecic, Mary Ellen; Stern, Lawrence C.; Gerber, Nicholas
CORPORATE SOURCE: Coll. Med., Ohio State Univ., Columbus, OH, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1993), 264(3), 1071-8
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hind-limb unloading by tail suspension of **rats**, an established model of simulated microgravity, was used to examine the efficacy of aminohydroxybutane **bisphosphonate** (AHBuBP) and clenbuterol in

preventing **bone loss** and muscle atrophy, resp. Male Sprague-Dawley **rats** (299-372 g) were randomized into six groups of six: 1) unsuspended, saline, 2) unsuspended, saline, pair fed with group 3, 3) suspended, saline, 4) suspended, 0.03 mg/kg/day .times. 2 of AHBuBP, 5) suspended, 0.3 mg/kg/day .times. 2 of AHBuBP and 6) suspended, 0.3 mg/kg/day .times. 2 of AHBuBP + clenbuterol (0.5 mg/kg/day i.p. .times. 6, then 1 mg/kg/day i.p. .times. 6). Animals in groups 3 to 6 were tail suspended for 14 days from a system of double pulleys and allowed free mobility with their hind limbs unloaded. On days -2 and -1, before suspension on day 0, all **rats** received a single s.c. injection of either 2 mL/kg of normal saline (vehicle) or AHBuBP. All **rats** were tested for exercise tolerance before day -2 and on day 10, and grip strength before day -2 and on day 13. On day 14, the **rats** were euthanized and their humeri, tibias and femurs analyzed in vitro for bone d. (by single-photon absorptiometry), strength and stiffness (by 3-point bending). Muscles were analyzed for wt., protein concn. and enzyme activity. Pair feeding had no effect other than on food consumption and body wt. AHBuBP caused a dose-dependent increase in bone d. in humeri, tibias and femurs, even in tail-suspended **rats**, relative to control unsuspended animals, with no significant difference in bone strength or stiffness between AHBuBP groups and unsuspended animals. In tail-suspended **rats**, clenbuterol ameliorated skeletal muscle atrophy, enhanced exercise tolerance and caused cardiac hypertrophy.

L24 ANSWER 50 OF 59 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1993:140340 HCAPLUS
DOCUMENT NUMBER: 118:140340
TITLE: Parathyroid hormone is more effective than estrogen or **bisphosphonates** for restoration of lost bone mass in ovariectomized **rats**
AUTHOR(S): Wronski, T. J.; Yen, C. F.; Qi, H.; Dann, L. M.
CORPORATE SOURCE: Coll. Vet. Med., Univ. Florida, Gainesville, FL, 32610, USA
SOURCE: Endocrinology (1993), 132(2), 823-31
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The study was designed to compare the **therapeutic** efficacy of estrogen, the **bisphosphonate** risedronate (NE 58095), and PTH for restoration of lost bone mass in osteopenic, ovariectomized (OVX) **rats**. In addn., the skeletal effects of these single **treatments** were compared to those of concurrent **treatments** with PTH + estrogen or PTH + NE 58095. OVX **rats** were untreated for the first 4 wk postovariectomy to allow for the development of moderate tibial osteopenia. These animals were then subjected to the various **treatments** for periods of 5, 10, and 15 wk. Their proximal tibias were processed undecalcified for quant. bone histomorphometry. **Treatment** of osteopenic OVX **rats** with estrogen or NE 58095 alone depressed bone turnover and prevented addnl. cancellous **bone loss** from occurring during the **treatment** period. However, these **therapeutic** agents failed to restore lost bone in OVX **rats** to control levels. In contrast, OVX **rats treated** with PTH alone exhibited a marked stimulation of bone formation which resulted in augmentation of cancellous bone mass to a level 2-fold greater than that of vehicle-**treated** control **rats**. Concurrent **treatment** of OVX **rats** with PTH + estrogen as well as PTH + NE 58095 also effectively reversed cancellous osteopenia in OVX **rats**, but did not appear to be more beneficial to the estrogen-deplete skeleton than

treatment with PTH alone. Apparently, PTH is a powerful stimulator of bone formation and completely restores lost cancellous bone in osteopenic OVX **rats**. Furthermore, the bone anabolic effects of PTH are much more pronounced than those of estrogen or **bisphosphonates**. These findings in an animal model of estrogen depletion provide support for PTH as a potentially effective **treatment** for oophorectomized and postmenopausal women with established osteoporosis.

L24 ANSWER 51 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:94282 HCAPLUS
DOCUMENT NUMBER: 118:94282
TITLE: Effects of a **bisphosphonate** on experimental periodontitis in monkeys
AUTHOR(S): Brunsvold, Michael A.; Chaves, Eros S.; Kornman, Kenneth S.; Aufdemorte, Thomas B.; Wood, Robert
CORPORATE SOURCE: Health Sci. Cent., Univ. Texas, San Antonio, TX, USA
SOURCE: Journal of Periodontology (1992), 63(10), 825-30
CODEN: JOPRAJ; ISSN: 0022-3492
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Bisphosphonates** have been shown to increase bone mass in estrogen-deficient **patients** by inhibiting osteoclast activity. The purpose of this study was to measure clin. and radiog. effects of a **bisphosphonate** on periodontitis development in monkeys. Twenty-seven (27) adult cynomolgus monkeys were studied. After quarantine, baseline data were obtained including plaque index, gingival index, clin. probing depth measurements, and intraoral radiographs. Standardized radiographs were analyzed for quant. changes in bone d. using a computer assisted densitometric (CADIA) system. Animals were divided into 3 groups to receive 1 of the 3 **treatment** agents; these agents consisted of two levels of the test drug (alendronate) and a saline placebo. Agents were injected in the saphenous vein of the lower leg every 2 wk for 16 wk. One week after the initiation of **treatment** agent injections, mandibular right molars and premolars were ligated with 3-0 silk sutures to induce periodontitis. Ligated teeth were also inoculated with Porphyromonas gingivalis to insure a significant etiol. challenge. Nonligated homologous teeth served as controls. Clin. measurements and radiographs were repeated at 8 and 16 wk after ligation. The **bisphosphonate** at a concn. of 0.05 mg/kg significantly retarded the progression of periodontitis as measured by bone d. changes. The higher level dose of the test drug did not differ from placebo with respect to **loss** of **bone** d. Clin. indexes were not affected significantly by the test drugs. Drugs that alter bone metab. may offer a new approach to the **treatment** of periodontal disease.

L24 ANSWER 52 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:143650 HCAPLUS
DOCUMENT NUMBER: 116:143650
TITLE: Aminohydroxybutane **bisphosphonate** prevents **bone loss** in a **rat** model of simulated weightlessness
AUTHOR(S): Apseloff, Glen; Girten, Beverly; Walker, Monica; Shepard, Dale R.; Matkovic, Velimir; Stern, Lawrence S.; Gerber, Nicholas
CORPORATE SOURCE: Coll. Med., Ohio State Univ., Columbus, OH, 43210, USA
SOURCE: Current Therapeutic Research (1991), 50(6), 794-803
CODEN: CTCEA9; ISSN: 0011-393X

Search completed by David Schreiber. 308-4292

DOCUMENT TYPE: Journal
LANGUAGE: English
AB An established model of simulated weightlessness was used to study the efficacy of aminohydroxybutane **bisphosphonate** (AHBuBP) in preventing **bone loss**. **Administration** of AHBuBP resulted in increased bone d. in tibias and femurs, even in tail-suspended **rats**, relative to control unsuspended animals, while mech. studies demonstrated significant weakening of bone only in suspended saline-injected **rats**.

L24 ANSWER 53 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:120857 HCAPLUS
DOCUMENT NUMBER: 116:120857
TITLE: Inhibition of bone resorption by **bisphosphonates**: interactions between **bisphosphonates**, osteoclasts, and bone
AUTHOR(S): Flanagan, Adrienne M.; Chambers, Timothy J.
CORPORATE SOURCE: Med. Sch., St. George's Hosp., London, SW17 0RE, UK
SOURCE: Calcified Tissue International (1991), 49(6), 407-15
CODEN: CTINDZ; ISSN: 0171-967X

DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Bisphosphonates** are nonbiodegradable pyrophosphate analogs that are being used increasingly to inhibit bone resorption in disorders characterized by excessive **bone loss**. The authors previously found that dichloromethylene **bisphosphonate** (Cl2MBP) inhibits bone resorption through injury to the cells that resorb Cl2MBP-contaminated surfaces, 3-amino-1-hydroxypropylidene-1,1-**bisphosphonate** (AHPrBP) is a more potent inhibitor of bone resorption in vivo, and the authors attempted to identify a step in the resorptive pathway that accounts for this increased potency. It was found that when osteoclasts, isolated from neonatal **rat** long bones, were incubated on bone slices in the presence of **bisphosphonates**, AHPrBP was less, rather than more potent as a resorption-inhibitor than Cl2MBP. The greater sensitivity of resorption to AHPrBP in vivo could neither be attributed to an effect of AHPrBP on the ability of osteoblastic cells to stimulate resorption in response to calcium-regulating hormones in vitro nor to an effect on osteoclast generation: osteoclast formation was unaffected by concns. of AHPrBP 10-fold higher than those of Cl2MBP which inhibit bone resorption in the bone slice assay. No evidence for impaired osteoclast generation in vivo in AHPrBP-**treated rats** was found. These results suggest that the comparisons of potency in vitro do not include all the factors responsible for detg. **bisphosphonate** potency in vitro. Because **bisphosphonates** owe the specificity of their actions to their ability to bind to bone surfaces, the authors performed expts. using bone slices that had been immersed in **bisphosphonates** before use. Bone resorption was virtually abolished on bone slices preincubated in 10-3 M AHPrBP. Inhibition was assocd. with degenerative changes in osteoclasts and a more rapid decrease in the no. remaining on the bone surface than occurred with Cl2MBP. The effect was specific for osteoclasts, could be prevented if bone resorption was suppressed by calcitonin, and was not seen in osteoclasts incubated in AHPrBP on plastic coverslips. These observations suggest that AHPrBP inhibits bone resorption through injury to osteoclasts when they solubilize **bisphosphonate**-contaminated bone. The concn. of AHPrBP used in the preincubation phase could be reduced by an order of magnitude if the vol. of the AHPrBP soln. was correspondingly increased. This implies that the concn. of **bisphosphonate** is less relevant to potency

comparisons than the d. of **bisphosphonate** on the bone surface. The latter will be strongly influenced in vivo not only by affinity for bone but by the pharmacokinetic and other properties of the compd.

L24 ANSWER 54 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:464499 HCAPLUS
DOCUMENT NUMBER: 115:64499
TITLE: The **bisphosphonate** alendronate (MK-217) inhibits **bone loss** due to ovariectomy in **rats**
AUTHOR(S): Seedor, J. Gregory; Quartuccio, Helen A.; Thompson, David D.
CORPORATE SOURCE: Dep. Bone Biol. Osteoporosis Res., Merck, Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Journal of Bone and Mineral Research (1991), 6(4), 339-46
CODEN: JBMREJ; ISSN: 0884-0431
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Estrogen deficiency in **mammals** is known to increase bone turnover and result in reduced bone mass. The **bisphosphonate**, 4-amino-1-hydroxybutylidene-1,1-**bisphosphonic** acid disodium salt, alendronate (MK-217), is a potent inhibitor of bone resorption and was evaluated in this study for its ability to inhibit **bone loss** following ovariectomy in **rats**. Alendronate (MK-217) was effective in inhibiting **bone loss** due to estrogen deficiency in **rats**, and the magnitude of its effect was related primarily to the total amt. of compd. **administered** rather than the frequency of its **administration**.

L24 ANSWER 55 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:429628 HCAPLUS
DOCUMENT NUMBER: 115:29628
TITLE: Preparation of acyloxymethyl esters of **bisphosphonic** acids as bone resorption inhibitors
INVENTOR(S): Saari, Walfred S.; Anderson, Paul S.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 416689	A2	19910313	EP 1990-202312	19900829
EP 416689	A3	19910626		
EP 416689	B1	19951129		
R: CH, DE, FR, GB, IT, LI, NL				
US 5227506	A	19930713	US 1990-549497	19900712
CA 2024694	AA	19910307	CA 1990-2024694	19900905
JP 03106893	A2	19910507	JP 1990-234649	19900906
JP 07119230	B4	19951220		
LV 11473	B	19961220	LV 1996-33	19960206
			US 1989-403411	19890906

PRIORITY APPLN. INFO.:
OTHER SOURCE(S): MARPAT 115:29628
AB (YO)2P(O)CRR1P(O)(OY)OCH2O2CR2 [R = H, halo, OH; R1 = (substituted) alkyl,

Search completed by David Schreiber. 308-4292

cycloalkyl, halo, piperidinyl, pyrrolidinyl, alkylthio, PhS; R2 = alkyl; Y = H, CH2O2CR2] were prepd. Thus, H2N(CH2)3C(PO3H2)2OH di-Na salt in THF/H2O was **treated** with PhCH2O2CCl to give 66% PhCH2O2CNH(CH2)3C(PO3H2)OH. The latter was **treated** with ClCH2O2CCMe3 and (Me2CH)2NEt in DMF to give a separable mixt. of di- and triesters. The diester was hydrogenolyzed in EtOH over Pd/C to give H2N(CH2)3C(PO3H2)2OH di(pivaloyloxymethyl) ester. The latter at 0.5 mg/kg s.c. in **rats** reduced immobilization-induced hind limb **bone loss** from 27.6 mg (controls) to 7.3 mg.

L24 ANSWER 56 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:400053 HCAPLUS
DOCUMENT NUMBER: 115:53
TITLE: Pamidronate. A review of its pharmacological properties and **therapeutic** efficacy in resorptive bone disease
AUTHOR(S): Fitton, Andrew; McTavish, Donna
CORPORATE SOURCE: Adis Drug Inf. Serv., Auckland, N. Z.
SOURCE: Drugs (1991), 41(2), 289-318
CODEN: DRUGAY; ISSN: 0012-6667
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 148 refs. Pamidronate [aminohydroxypropylidene **diphosphonate** disodium (APD), disodium pamidronate] is an orally and i.v. active amino-substituted **bisphosphonate** which produces potent and sp. inhibition of bone resorption at doses devoid of any significant detrimental effect on bone growth and mineralization. Clin. trials indicate that pamidronate is effective in a variety of conditions characterized by pathol. enhanced bone turnover, including Paget's disease, hypercalcemia of malignancy, osteolytic bone metastasis, steroid-induced osteoporosis and idiopathic osteoporosis. Pamidronate is highly effective in restoring normocalcemia in **patients** with hypercalcemia of malignancy assocd. with bone metastases but, in common with other **bisphosphonates**, is marginally less effective against humoral hypercalcemia of malignancy. Comparative studies in this area have suggested that, at **therapeutic** doses, pamidronate has a more pronounced calcium-lowering action than etidronate (etidronic acid) and clodronate (clodronic acid) and provides a longer period of normocalcemic remission. In Paget's disease arrest and, in some **patients**, reversal of the progression of osteolytic lesions by pamidronate is assocd. with a sustained redn. in bone pain, improved mobility and a possible reduced risk of bone fracture. In **patients** with osteolytic bone metastasis pamidronate reduces skeletal morbidity and slows the progression of metastatic bone destruction. Long term use of low-dose pamidronate in conjunction with conventional antiosteoporotic **therapy** may halt **bone loss** in steroid-induced and idiopathic osteoporosis. Pamidronate appears to represent a valuable addn. to the drugs currently available for the **treatment** of symptomatic Paget's disease and cancer-assocd. hypercalcemia, and shows promise in the **treatment** of osteolytic bone metastasis and osteoporosis.

L24 ANSWER 57 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:229549 HCAPLUS
DOCUMENT NUMBER: 112:229549
TITLE: Hyperostosis induced by the **bisphosphonate** (2-PEBP) in the oophorectomized **rat**
AUTHOR(S): Movsowitz, Colin; Epstein, Sol; Fallon, Michael; Ismail, Firhaad; Thomas, Steven

Search completed by David Schreiber. 308-4292

Kwon 10/088,884

CORPORATE SOURCE: Div. Endocrinol. Metab., Albert Einstein Med. Cent., Philadelphia, PA, 19141, USA
SOURCE: Calcified Tissue International (1990), 46(3), 195-9
CODEN: CTINDZ; ISSN: 0171-967X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To prevent the high-turnover bone remodeling assocd. with acute estrogen deficiency, the **bisphosphonate** [2-(2-pyridinyl)ethylidene-BP] (2-PEBP) was **administered** to oophorectomized (OX) **rats**. Group (Gp) A was sham operated, Gp B was OX, and Gp C received 2-PEBP (1.72 mg/kg/day) i.p. for 3 days commencing 4 days postoophorectomy. Oophorectomy was confirmed with serum estradiol measurements. Blood samples were collected on days -7, 0, 7, 14, 21, and 28 for ionized calcium (Ca2+), parathyroid hormone (PTH) and serum bone gla protein (BGP). **Rats** received tetracycline for bone histomorphometric labeling. All results were compared to Gp A. Body wt. increased in Gps B and C. There was no difference in Ca2+, and PTH levels in Gps B and C were similar to Gp A. BGP levels were higher on day 28 in Gp B. In Gp C, BGP levels were decreased on days 7, 21, and 28. Gp B revealed increased **bone** turnover without **loss** of **bone** vol. (BV/TV). BV/TV was increased in Gp C despite a decrease in parameters of bone formation and normal osteoclast no. In conclusion, 2-PEBP in the OX **rat** inhibited bone resorption more than formation with resultant hyperostosis. Serum BGP appeared to be a good marker of the changes obsd. on bone histomorphometry.

L24 ANSWER 58 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:527227 HCAPLUS
DOCUMENT NUMBER: 111:127227
TITLE: Endocrine and pharmacological suppressors of bone turnover protect against osteopenia in ovariectomized **rats**
AUTHOR(S): Wronski, T. J.; Dann, L. M.; Scott, K. S.; Crooke, L. R.
CORPORATE SOURCE: Coll. Vet. Med., Univ. Florida, Gainesville, FL, 32610, USA
SOURCE: Endocrinology (1989), 125(2), 810-16
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
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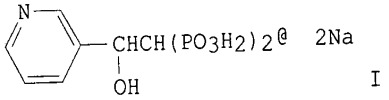

I

AB Sham-operated control and ovariectomized (OVX) **rats** were **treated** intermittently with vehicle alone, estrogen, or the **diphosphonate** compds. EHDP and NE 58095 (I) for 35 or 70 days after surgery. Their proximal tibiae were processed undecalcified for quant. bone histomorphometry. Vehicle-**treated** OVX **rats** were characterized by decreased cancellous bone vol. and 3-4-fold increases in osteoblast surface, osteoclast surface, bone formation **rate**, and bone resorption **rate**. **Treatment** of OVX **rats** with estrogen and I provided complete protection

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against **bone loss** and depressed all of the above indexes of bone turnover. OVX **rats treated** with EHDP exhibited at least partial protection against **bone loss** and decreased **bone** turnover. EHDP induced a mild mineralization defect, as indicated by a prolonged mineralization lag time at a tibial endocortical surface. I did not impair bone mineralization. Apparently, endocrine and pharmacol. suppressors of bone turnover prevent the development of osteopenia during the early stages of estrogen deficiency.

L24 ANSWER 59 OF 59 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:197606 HCAPLUS
DOCUMENT NUMBER: 102:197606
TITLE: Influence of **treatment** with APD-**bisphosphonate** on the bone lesions in **mouse** 5T2 multiple myeloma
AUTHOR(S): Radl, Jiri; Croese, Jan W.; Zurcher, Chris; Van den Enden-Vieveen, Margit H. M.; Brondijk, Roelfien J.; Kazil, Marketa; Haaijman, Joost; Reitsma, Pieter H.; Bijvoet, Olav L. M.
CORPORATE SOURCE: Inst. Exp. Gerontol., TNO, Rijswijk, Neth.
SOURCE: Cancer (New York, NY, United States) (1985), 55(5), 1030-40
CODEN: CANCAR; ISSN: 0008-543X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the **treatment** of multiple myeloma (MM) with (3-amino-1-hydroxypropylidene) 1,1-**bisphosphonate** (APD **bisphosphonate**) [**57248-88-1**] on bone destruction, the dissemination pattern of the MM, and toxicity for normal and malignant cells were investigated in an animal model, the 5T2 MM. This **mouse** MM very closely resembles the **human** disease, including the typical bone lesions. **Treatment** of the 5T2 MM with APD **bisphosphonate** protected the **mice** against **bone loss**. It seemed that the **treatment** with APD **bisphosphonate** not only diminished the bone destruction by the MM but also led to the formation of new bone in already-affected bone tissue. The growth pattern of the MM was not substantially influenced by the **treatment**, even though there was an indication that the compd. exerted some cytotoxic effect on the MM cells.

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FILE LAST UPDATED: 15 May 2003 (20030515/ED)

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=> d que l31
L25 15 SEA FILE=HCAPLUS DOTMP AND BONE
L26 6 SEA FILE=HCAPLUS ?METHYLENE? AND ?PHOSPHONIC? AND ?PYRIDIN? AND ?DIAZA?
L27 35 SEA FILE=HCAPLUS ?TETRAAZA? AND ?TETRADECA? AND ?PHOSPHON?
L28 2 SEA FILE=HCAPLUS L27 AND ?BICYCLO?
L29 0 SEA FILE=HCAPLUS L28 AND BONE#
L30 5 SEA FILE=HCAPLUS ?METHYLENEPHOSPHON? AND ?AMINOMETHYL? AND ?PYRIDIN?
L31 27 SEA FILE=HCAPLUS L25 OR L26 OR (L28 OR L29 OR L30)

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L31 ANSWER 1 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:353066 HCAPLUS
TITLE: Dosimetry of High Dose Skeletal Targeted Radiotherapy (STR) with 166Ho-**DOTMP**
AUTHOR(S): Breitz, Hazel; Wendt, Richard; Stabin, Michael; Bouchet, Lionel; Wessels, Barry
CORPORATE SOURCE: NeoRx Corporation, Seattle, WA, USA
SOURCE: Cancer Biotherapy & Radiopharmaceuticals (2003), 18(2), 225-230
CODEN: CBRAFJ; ISSN: 1084-9785
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A study was undertaken to det. the max. tolerated dose of 166Ho-**DOTMP** that could be administered safely, without neg. impacting marrow re-engraftment, in patients with multiple myeloma treated with melphalan prior to transplant. Ho-166 **DOTMP** is a tetraphosphonate that localizes rapidly to **bone** surface. The Ho-166 phys. half-life is 26.8 h and the max. beta energy is 1.8 MeV. Std. dosimetry models were adapted for radiation absorbed dose ests. using data obtained from whole body counting of the low abundance photons

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emitted by 166Ho. Eighty-three patients received high dose 166Ho-**DOTMP** followed by melphalan and transplant of peripheral blood stem cells. Twenty-five patients also received 8 Gy total body radiation (TBI). Dosages administered ranged from 460 to 4476 mCi 166Ho-**DOTMP**. Marrow dose was derived using the assumption that all radioactivity not excreted by 20 h was localized to the **bone** surfaces, and applying the Eckerman **bone** and marrow dose model to the calcd. **bone** residence times. The dosimetry of the urinary bladder and kidneys was important because of the rapid excretion of the non-targeted radioactivity via the urinary pathway. The dynamic bladder model was used for bladder wall surface dose, and the ICRP 53 kinetic model was used to model kidney kinetics with an addnl. blood component included. Marrow doses ranged from 13 to 59 Gy and successful hematapoietic recovery occurred. Bladder doses ranged from 4.7 to 157 Gy. Hemorrhagic cystitis occurred in some patients who received more than 40 Gy to the bladder wall surface. Bladder irrigation was successful in protecting patients from bladder toxicity. Kidney doses ranged from 0.5-7.9 Gy. Kidney toxicity in the form of thrombotic microangiopathy. with renal dysfunction was obsd., with the severity being related to Ho-166-**DOTMP** radiation dose and probably the dose rate as well. In a future trial, kidney dosimetry will be assessed using early serial gamma camera imaging and modifications will be implemented to reduce renal toxicity.

L31 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:235322 HCAPLUS
TITLE: Synthesis, crystal structure and chemical stability of bismuth(iii) complexed with 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (H8DOTMP)
AUTHOR(S): Hassfjell, Sindre; Kongshaug, Kjell Ove; Romming, Christian
CORPORATE SOURCE: Department for Reservoir and Exploration Technology, Institute for Energy Technology, P.O. Box 40, Norway
SOURCE: Dalton Transactions (2003), (7), 1433-1437
CODEN: DTARAF; ISSN: 1477-9226
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The potential use of the .alpha.-particle emitting compds. 212/213Bi-**DOTMP** and 212Pb-**DOTMP** in therapy of **bone** -assocd. cancers, and medical interest in bismuth compds., motivated this study. Syntheses of the Bi(iii) and Pb(ii) complexes of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (H8DOTMP) are reported. Extensive pH-stability was found for both complexes, in the pH range 0-13 for Bi-**DOTMP** and pH 4-14 for Pb-**DOTMP**. Furthermore, both complexes formed within 1 min in the pH range 6-10 at 10 .mu.M metal-ion and 15 .mu.M **DOTMP**. Single crystals of [NaBi(H4DOTMP)] and polycryst. [Bi(H5O2)(H4DOTMP)] were formed and characterized by single crystal and powder X-ray diffraction methods, resp. The structure of the anion was found in both salts to exhibit a square antiprismatic eight-coordination with a four-fold axis of symmetry.

L31 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:113543 HCAPLUS
DOCUMENT NUMBER: 138:155350
TITLE: Phosphonic acid-stabilized peroxotungsten catalysts used for oxidation of organic compounds with hydrogen peroxide

Search completed by David Schreiber 308-4292

Kwon 10/088,884

INVENTOR(S): Bischoff, Stefan; Kant, Michael
PATENT ASSIGNEE(S): Institut Fuer Angewandte Chemie Berlin-Adlershof E.V., Germany
SOURCE: Ger. Offen., 8 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10136884	A1	20030213	DE 2001-10136884	20010724

PRIORITY APPLN. INFO.: DE 2001-10136884 20010724
OTHER SOURCE(S): MARPAT 138:155350

AB Phosphonic acid-stabilized peroxotungsten catalysts comprise a peroxotungsten compd. and one or more phosphonic acids of the general formula [Y-(CH2)p]nN[CHq(PO3H2)3-q]3-n or their alkali metal or ammonium salts, where n is 0, 1 or 2; q is 1 or 2; p is 0-16; Y is H, OH, OR1, R1CO, R1COO, CHO, COOH, COOR1, SO3H, F, Cl, Br or R1R2N; R1 and R2 are C1-18-alkyl, C5-12-cycloalkyl, C6-18-homo or heteroaryl or C6-24-alkylheteroaryl groups; Y is not H when simultaneously q is 2 and n is 2, the phosphorus to tungsten ratio being from 1:50 to 10:1. The catalyst systems can addnl. comprise N-(C8-24-alkyl)**pyridinium** salts or onium salts used as phase transfer reagents. The phosphonic acid-stabilized peroxotungsten catalysts are used for oxidn., epoxidn., dihydroxylation, oxidative bond cleavage, Baeyer-Villiger oxidn. with hydrogen peroxide of org. compds., such as hydroxy compds. and unsatd. compds. Thus, allyl alc. was dihydroxylated at 45.degree. and pH 1.5 using hydrogen peroxide and a catalyst system comprising disodium tungstate dihydrate and N-hydroxyiminobis(**methylenephosphonic** acid). Glycerol was produced in 95% yield and 93% selectivity.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:67583 HCAPLUS
TITLE: **Phosphonoacetic** acid as a building block in supramolecular chemistry: salts with organic polyamines
AUTHOR(S): Bowes, Katharine F.; Ferguson, George; Lough, Alan J.; Zakaria, Choudhury M.; Glidewell, Christopher
CORPORATE SOURCE: School of Chemistry, University of St Andrews, Fife, St Andrews, KY16 9ST, UK
SOURCE: Acta Crystallographica, Section B: Structural Science (2003), B59(1), 87-99
CODEN: ASBSDK; ISSN: 0108-7681
PUBLISHER: Blackwell Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Phosphonoacetic** acid, (HO)2P(O)CH2COOH, forms adducts with a range of amines. The acid component in these adducts may be the neutral mol. C2H5O5P, the mono-anion (C2H4O5P)- or the di-anion (C2H3O5P)2-. The substructure formed by the acid component takes the form of simple chains in compds. (1)-(3), which are the 1:1 adducts formed with 1,4-**diazabicyclo**[2.2.2]octane, 4,4'-bipyridyl and 1,3-trimethylenedipiperidine, resp. These adducts contain C2H5O5P, (C2H4O5P)- and (C2H3O5P)2-, resp., although (3) is solvated by a mixt. of methanol and water. The (C2H4O5P)- anion substructure in (4), which is the adduct

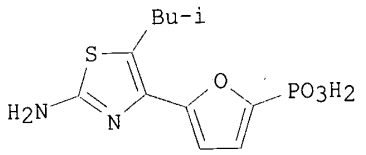
formed with meso-5,5,7,12,12,14-hexa-C-methyl-1,4,8,11-**tetraazacyclotetradecane**, is a chain of spiro-fused rings, while the substructure in (5), which is the adduct formed with 2,2'-dipyridylamine, is a chain of edge-fused rings. In (6), the adduct formed with 1,2-bis(4'-pyridyl)ethane, the anion substructure is two-dimensional. The chain substructures are linked by the amine units into two-dimensional structures in (1) and (4) and into three-dimensional frameworks in (2), (3) and (5), while the anion sheets in (6) are likewise linked by the amine units into a three-dimensional framework.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:921901 HCAPLUS
DOCUMENT NUMBER: 138:4695
TITLE: Preparation of heteroaromatic phosphonates as fructose 1,6-bisphosphatase inhibitors
INVENTOR(S): Dang, Qun; Kasibhatla, Srinivas Rao; Reddy, K. Raja; Erion, Mark D.; Reddy, M. Rami; Agarwal, Atul
PATENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA
SOURCE: U.S., 129 pp., Cont.-in-part of U.S. Provisional Ser. No. 135,504.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6489476	B1	20021203	US 1999-389698	19990903
PRIORITY APPLN. INFO.:			US 1998-135504P P	19980909
			US 1998-111077P P	19981207

GI



II

AB The title compds. R5XP(O)(YR1)2 [I; wherein X = (un)substituted (cyclic) linking group between R5 and P via 1-4 atoms, including 0-1 N, O, or S atoms; or X = urea or carbamate; Y = independently O or NR6; when Y = O, R1 = H, alkyl, (un)substituted (alkyl)aryl or alicyclic, C(R2)2OC(O)NR22, NR2C(O)R3, C(R2)2OC(O)R3, etc.; when Y = NR6, R1 = H, [C(R2)2]qC(O)OR3, C(R4)2C(O)OR3, [C(R2)2]qC(O)SR3, cycloalkylene-C(O)OR3, etc.; R2 = H or R3; R3 = (ar)alkyl, aryl, or alicyclic; R4 = H, alkyl, etc.; R5 = (un)substituted benzothiazolyl, benzoxazolyl, thiazolyl, (is)oxazolyl, imidazolyl, pyrazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, etc.; R6 = H, (acyloxy)alkyl, alkoxycarbonyloxyalkyl, or acyl; q = 1-2], and their prodrugs, were prepd. via high throughput and std. synthetic methods. Compds. I and their prodrugs were tested for a variety of biol.

activities including inhibition of fructose 1,6-bisphosphatase (FBPase) and activity toward AMP binding enzymes, such as adenosine kinase. Compds. of the invention are useful in the treatment of diabetes and other diseases where inhibition of gluconeogenesis, control of blood glucose levels, redn. in glycogen storage, or redn. in insulin levels is beneficial. Thus, the phosphonofuranylthiazole (II) was prepd. and tested for inhibition of human liver FBTase (IC50 = 0.025 .mu.M), inhibition of gluconeogenesis (IC50 = 2.5 .mu.M), and blood glucose lowering (65% i.v.).
REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:849373 HCAPLUS
DOCUMENT NUMBER: 137:358081
TITLE: Diagnostic imaging compositions, their methods of synthesis, and use
INVENTOR(S): Li, Chun; Wen, Xiaoxia; Wu, Qing-Ping; Wallace, Sydney; Ellis, Lee M.
PATENT ASSIGNEE(S): Board of Regents, the University of Texas System, USA
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002087498	A2	20021107	WO 2002-US12510	20020419
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2002197261	A1	20021226	US 2002-126369	20020419
US 2003003048	A1	20030102	US 2002-126216	20020419
PRIORITY APPLN. INFO.:			US 2001-286453P	P 20010426
			US 2001-334969P	P 20011204
			US 2001-343147P	P 20011220

AB Conjugate mols. comprising a ligand bonded to a polymer are disclosed. One such conjugate mol. comprises a ligand bonded to a polymer, a chelating agent bonded to the polymer, and a radioisotope chelated to the chelating agent. The conjugate mols. may be useful in detecting and/or treating tumors or biol. receptors. These conjugate mols. may be synthesized without the necessity of preactivation of the ligand using an SCN-polymer-chelating agent precursor. Conjugate mols. incorporating an annexin V ligand are particularly useful for visualizing apoptotic cells. Conjugate mols. incorporating a C225 ligand are particularly useful for targeting tumors expressing EGFR.

L31 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:836018 HCAPLUS
DOCUMENT NUMBER: 137:348508
TITLE: High-dose 166Ho-**DOTMP** in myeloablative treatment of multiple myeloma: pharmacokinetics,

Kwon 10/088,884

biodistribution, and absorbed dose estimation

AUTHOR(S): Rajendran, Joseph G.; Eary, Janet F.; Bensinger, William; Durack, Larry D.; Vernon, Cheryl; Fritzberg, Alan

CORPORATE SOURCE: Department of Radiology, University of Washington, Seattle, WA, USA

SOURCE: Journal of Nuclear Medicine (2002), 43(10), 1383-1390
CODEN: JNMEAQ; ISSN: 0161-5505

PUBLISHER: Society of Nuclear Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thirty-two patients with multiple myeloma were treated with high doses of 166Ho-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid (**DOTMP**) and were a subset of patients enrolled in a multicenter phase I/II dose escalation myeloablative trial. 166Ho with .beta.-emission (half-life, 26.8 h; .beta.-particle energies, 1.85 MeV [51%] and 1.77 MeV [48%]; .gamma.-photons, 80.6 keV [6.6%] and 1.38 MeV [0.9%]) was complexed to **DOTMP**, a macrocyclic tetraphosphonate. Pharmacokinetics, dosimetry, and biodistribution were studied. Patients were treated at escalating dose levels of 20, 30, and 40 Gy to the **bone** marrow in combination with high-dose melphalan, with or without total-body irradn., to evaluate toxicity and efficacy. After infusion with 1,110 MBq (30 mCi) of 166Ho-**DOTMP** for evaluation of biodistribution and dosimetry calcn., patients received the calcd. amt. of radioactivity for therapy in a single administration based on estd. dose calcns. Thirty-two patients participated in the study and were then treated. The av. amt. of administered radioactivity was 74.3 GBq (2,007 mCi) (range, 21.5-147.5 GBq [581-3,987 mCi]) of 166Ho-**DOTMP**. 166Ho-**DOTMP** has phys. and pharmacokinetic characteristics compatible with high-dose myeloablative treatment of multiple myeloma.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:444931 HCAPLUS
DOCUMENT NUMBER: 138:69067
TITLE: 177Lu-labeled cyclic polyaminophosphonates as potential agents for **bone** pain palliation

AUTHOR(S): Das, Tapas; Chakraborty, Sudipta; Unni, P. R.; Banerjee, Sharmila; Samuel, Grace; Sarma, H. D.; Venkatesh, Meera; Pillai, M. R. A.

CORPORATE SOURCE: Radiopharmaceuticals Division, Bhabha Atomic Research Centre, Mumbai, 400 085, India

SOURCE: Applied Radiation and Isotopes (2002), 57(2), 177-184
CODEN: ARISEF; ISSN: 0969-8043

PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 177Lu (T1/2=6.71 d, E.beta.(max)=497 keV) has radionuclidic properties suitable for use in palliative therapy of **bone** pain due to metastasis. 177Lu was produced in high-specific activity (3-4 TBq/g) and excellent radionuclidic purity (100%) by thermal neutron bombardment of natural Lu target. Two cyclic tetraaminomethylene phosphonate ligands, namely **DOTMP** and CTMP were synthesized and radiolabeled with 177Lu. The 177Lu-**DOTMP** complex was formed with very high yield (>99%) and showed excellent stability (up to 40 d at room temp.). Biodistribution of 177Lu-**DOTMP** was carried out in Wistar rats and the complex showed significant **bone** uptake (4.23%/g in femur and 5.23% in tibia at 3 h p. i.), rapid clearance from blood (no activity

Search completed by David Schreiber 308-4292

at 3 h p. i.) and min. uptake in soft tissues.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:291058 HCAPLUS
DOCUMENT NUMBER: 137:183085
TITLE: Advances in the pathogenesis and treatment of multiple myeloma
AUTHOR(S): Kraj, Maria
CORPORATE SOURCE: Klinika Hematol., Inst. Hematol. i Transfuzjol., Warsaw, 00-957, Pol.
SOURCE: Nowotwory, Journal of Oncology (2001), 51(5), 516-522
CODEN: NJOOAE
PUBLISHER: Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Genetic instability is a crit. factor in the pathogenesis of multiple myeloma. Translocations of the IgH locus, 14q32 seem to be an important universal event during the initiation of the disease whereas deletion of chromosome 13q14 affects disease progression and prognosis. The functional interplay between myeloma cells and the marrow stroma results in growth support of the tumor clone and is mediated by specific adhesive interactions and a paracrine network of several cytokines. Through induction of VEGF and bFGF cytokines myeloma cells trigger **bone** marrow vascularization resulting in increased microvessel d. which is directly related to the prognosis of the disease. By induction of RANKL expression and decrease of osteoprotegerin expression myeloma cells stimulate the generation of osteoclasts resulting in **bone** destruction. Some emerging novel biol. based therapies which target both the multiple myeloma cell and its microenvironment include: anti-angiogenesis approaches - vascular endothelial growth inhibitors, thalidomide and its potent immunomodulatory drug derivs. (CC 5013), proteasome inhibitor PS-341, arsenic trioxide, antibody-based immunotherapy against a myeloma cell-specific antigen HM1.24 (MoAb AHM), use of radiolabeled anti-CD138 monoclonal antibody for targeted radiotherapy and RANKL antagonists and RANKL antagonists. In the preparative regimen in autologous stem cell transplant the use of targeted radiotherapy with 166Ho-**DOTMP** or 153Sm-EDTMP is investigated. In an effort to decrease allogeneic transplant-related toxicity and to increase the graft vs. myeloma effect, a "mini-allogeneic" transplant with nonmyeloablative regimens and also with donor lymphocytes infusions after transplantation is used.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:71915 HCAPLUS
DOCUMENT NUMBER: 136:114841
TITLE: Method of radiotherapy
INVENTOR(S): Larsen, Roy H.; Henriksen, Gjermund
PATENT ASSIGNEE(S): Anticancer Therapeutic Inventions AS, Norway; Cockbain, Julian
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

Search completed by David Schreiber. 308-4292

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002005859	A2	20020124	WO 2001-GB2996	20010704
WO 2002005859	A3	20020906		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

NO 2000003457	A	20020107	NO 2000-3457	20000704
EP 1296722	A2	20030402	EP 2001-945519	20010704

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: NO 2000-3457 A 20000704
WO 2001-GB2996 W 20010704

AB The invention provides a method of radiation treatment of a human or non-human mammalian subject which comprises administering to said subject a therapeutically, prophylactically or pain-palliating amt. of a **bone**-targeting complex of an alpha-particle emitting thorium or actinium radionuclide, e.g. for the treatment of calcified tumors, **bone** tumors, bones, **bone** surfaces an soft tissues. 227Th was isolated from a 227Ac decay mixt. and 228Ra was used as generator material for 228Ac. Complexes of 227Th and 228Ac with DTMP and **DOTMP** were prepd. and their biodistribution, including **bone** uptake, detd. in mice.

L31 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:885836 HCAPLUS
DOCUMENT NUMBER: 136:2368
TITLE: A method of using a surrogate for a therapeutic agent to determine the therapeutic dose for **bone** marrow ablation therapy
INVENTOR(S): Wendt, Richard E., III; Simon, Jaime
PATENT ASSIGNEE(S): Steven McCullough, USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001091806	A2	20011206	WO 2001-US17608	20010531
WO 2001091806	C2	20020808		
WO 2001091806	A3	20021031		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2000-208154P P 20000531
AB A method of using a surrogate, preferably 99mTc-MDP, for a therapeutic agent (for example, 166Ho-EDTMP or preferably 166Ho-**DOTMP**) to calc. the dosimetry for the therapeutic dose for **bone** marrow ablation therapy is disclosed. The advantages of this use of a surrogate in lieu of the therapeutic agent is lower cost, less exposure to high radiation levels, and length of the half-life, while maintaining the biodistribution in the total skeleton.

L31 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:730521 HCAPLUS
DOCUMENT NUMBER: 135:293676
TITLE: Stable alkaline hair bleaching and coloring compositions and method for use thereof
INVENTOR(S): Dias, Louis Carlos
PATENT ASSIGNEE(S): The Procter + Gamble Company, USA
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072271	A2	20011004	WO 2001-US9213	20010323
WO 2001072271	A3	20020321		

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2000-537452 A 20000327
AB An alk. hair bleaching and coloring compn. comprising: (a) from about 0.01 to about 12, by wt., of at least one oxidizing agent; (b) from about 0.2 to about 20, by wt., of a buffering system, present in an amt. sufficient to generate a pH of the compn. in the range from about 5 to about 11, wherein said buffering system comprises at least one pH modifying ingredient selected from the group consisting of (i) borates buffers, (ii) alkalizing agents, and mixts. thereof; (c) from about 150 ppm to about 5,000 ppm of at least one stabilizer; and (d) from about 0.001 to about 5 , by wt., of at least one hair coloring agent. A hair bleaching and coloring compn. contained hydrogen peroxide 3, disodium tetraborate decahydrate 0.5, cyclohexane-1,2-diaminotetrakisphosphonic acid 0.1, alkyl dimethylamine oxide 0.3, cetearyl alc. 5, HC Red No. 3 0.3, HC Red No. 2 0.1, water and minors q.s. 100.

L31 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:407208 HCAPLUS
DOCUMENT NUMBER: 136:66276
TITLE: Synthesis, purification and biodistribution of 205Bi-**DOTMP**, visualizing **bone** deposition

patterns with autoradiography

AUTHOR(S): Hassfjell, S.; Ingebrigtsen, K.; Bruland, O. S.

CORPORATE SOURCE: Department of Chemistry, Nuclear Chemistry Section, University of Oslo, Oslo, N-0315, Norway

SOURCE: Nuclear Medicine and Biology (2001), 28(4), 425-433
CODEN: NMBIEO; ISSN: 0969-8051

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A HPLC system has been developed for carrier free and rapid delivery in a physiol. buffer of the .alpha.-particle emitting **bone**-seeking radiopharmaceutical 212Bi-**DOTMP**. 205Bi-**DOTMP** was synthesized and HPLC purified to mimic and visualize the deposition pattern in bony tissues of 212Bi-**DOTMP** by autoradiog. Inhomogeneous **bone** deposits were found with the highest concn. in the **bone** matrix, the endosteum and in the growth zones of young mice. Anal. of urine samples showed that 205Bi-**DOTMP** was cleared as an intact complex.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:900493 HCAPLUS

DOCUMENT NUMBER: 134:38949

TITLE: High dose radionuclide complexes for **bone** marrow suppression

INVENTOR(S): Abrams, Paul G.; Tatalick, Lauren M.; Thoelke, Kent R.; Bryan, James Kyle; John, Elizabeth K.; Hylaridés, Mark D.; Fritzberg, Alan R.

PATENT ASSIGNEE(S): Neorx Corporation, USA

SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000076556	A2	20001221	WO 2000-US16052	20000612
WO 2000076556	A3	20011011		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1191948	A2	20020403	EP 2000-944644	20000612
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003501488	T2	20030114	JP 2001-502887	20000612
US 2002176818	A1	20021128	US 2001-14335	20011211

PRIORITY APPLN. INFO.:

US 1999-139065P	P	19990611
US 1999-143780P	P	19990713
US 1999-149821P	P	19990819
WO 2000-US16052	W	20000612

OTHER SOURCE(S): MARPAT 134:38949

AB The present invention relates to a method of suppressing **bone** marrow (BM) and treating conditions that arise in or near **bone** such as cancer, myeloproliferative diseases, autoimmune diseases, infectious diseases, metabolic diseases or genetic diseases, with compns. having as their active ingredient a radionuclide complexed with a chelating agent such as macrocyclic aminophosphonic acid. Among the examples given are the prepn. and therapeutic application 166Ho-**DOTMP** in treating cancer.

L31 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:675084 HCAPLUS
DOCUMENT NUMBER: 134:12714
TITLE: [GdPCP2A(H2O)2]-: A Paramagnetic Contrast Agent Designed for Improved Applications in Magnetic Resonance Imaging
AUTHOR(S): Aime, Silvio; Botta, Mauro; Frullano, Luca; Crich, Simonetta Geninatti; Giovenzana, Giovanni; Pagliarin, Roberto; Palmisano, Giovanni; Sirtori, Federico Riccardi; Sisti, Massimo
CORPORATE SOURCE: Dipartimento di Chimica I.F.M., Universita di Torino, Turin, I-10125, Italy
SOURCE: Journal of Medicinal Chemistry (2000), 43(21), 4017-4024
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A novel ligand based on a **pyridine**-contg. macrocycle bearing two acetic arms and one **methylenephosphonic** arm (PCP2A) was synthesized. An efficient synthesis of PCP2A is based on the macrocyclization reaction between 2,6-bis(chloromethyl)**pyridine** and a 1,4,7-triazaheptane deriv. bearing a **methylenephosphonate** group on N-4. The Gd(III) complex of PCP2A displays characteristic properties which make it a very promising contrast agent for improved applications in magnetic resonance imaging. In fact it shows (i) a very high stability const. (log KGdPCP2A = 23.4) which should guarantee against the in vivo release of toxic free Gd(III) ions and free ligand mols. and (ii) a relaxivity that is .apprx.2 times higher than the values reported for contrast agents currently used in the clin. practice. Its high relaxivity is the result of the presence of two H2O mols. in the inner coordination sphere and a significant contribution from H2O mol.(s) H bonded to the phosphonate group. Also, the inner sphere H2O mols. are involved in an exchange with the bulk H2O which is relatively fast. This property is important for the attainment of an even higher relaxivity once the mol. reorientation rate of the [GdPCP2A(H2O)2]- moiety is lengthened by conjugation to a macromol. substrate.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:151755 HCAPLUS
DOCUMENT NUMBER: 132:171093
TITLE: Analgesic compositions for **bone** and joint diseases
INVENTOR(S): Jia, Wei; Zhu, Lin
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 8 pp.
CODEN: CNXXEV

Search completed by David Schreiber. 308-4292

DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1187350	A	19980715	CN 1998-100080	19980126
CN 1092962	B	20021023		

PRIORITY APPLN. INFO.: CN 1998-100080 19980126

AB Analgesic compns. for **bone** and joint diseases comprise nonradioactive metal ion-phosphonic acid complex. The metal ion is selected from Ga(III), Sn(IV), In(III), Sm(III), and Ce(IV); and phosphonic acid from EHDP, methanediphosphonic acid [MDP], ADEP, EDMP, NTMP, **DOTMP** and DTPMP.

L31 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:437991 HCAPLUS
DOCUMENT NUMBER: 127:47223
TITLE: 212Bi-**DOTMP**: an alpha particle emitting **bone**-seeking agent for targeted radiotherapy
AUTHOR(S): Hassfjell, S. P.; Bruland, Oe. S.; Hoff, P.
CORPORATE SOURCE: DEPARTMENT OF CHEMISTRY, UNIVERSITY OF OSLO, OSLO, N-0315, Norway
SOURCE: Nuclear Medicine and Biology (1997), 24(3), 231-237
CODEN: NMBIEO; ISSN: 0883-2897
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The synthesis and in vivo stability of the **bone**-seeking .alpha.-particle emitting compds. 212Bi-**DOTMP** and 212Pb/212Bi-**DOTMP** are described. 212Bi-**DOTMP**, injected IV into Balb/c mice, showed prominent **bone** localization and a rapid clearance from blood and other organs. Femur/blood ratios increased from 13 at 15 min up to 490 at 2.0 h postinjection. Enhanced uptake of 212Bi-**DOTMP** was demonstrated in regions with high **bone** turnover. A comparison between 212Bi-**DOTMP** and [153Sm]Sm-EDTMP showed essentially no differences in biodistribution. 212Pb/212Bi-**DOTMP** followed a similar biodistribution, except for slightly elevated levels of 212Bi in the kidneys. The present study has shown 212Bi-**DOTMP** to be an in vivo stable **bone**-seeking radiopharmaceutical with promising biol. properties for the treatment of sclerotic metastases and osteoblastic osteosarcoma.

L31 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:674768 HCAPLUS
DOCUMENT NUMBER: 126:72089
TITLE: Spectroscopic characterization and tissue imaging using site-selective polyazacyclic terbium(III) chelates
AUTHOR(S): Houlne, Michael P.; Agent, Tony S.; Kiefer, Garry E.; McMillan, Kenneth; Bornhop, Darryl J.
CORPORATE SOURCE: Dep. Chem. and Biochem., Texas Tech Univ., Lubbock, TX, 79409-1061, USA
SOURCE: Applied Spectroscopy (1996), 50(10), 1221-1228
CODEN: APSPA4; ISSN: 0003-7028
PUBLISHER: Society for Applied Spectroscopy
DOCUMENT TYPE: Journal
LANGUAGE: English

Search completed by David Schreiber. 308-4292

AB Polyazamacrocyclic chelates of terbium are shown to be useful in diagnostic medical imaging as tissue site-selective markers. Spectroscopic properties and biodistribution were studied for 3 terbium(III) species: 3,6,9-tris(**methylene phosphonic** acid Bu ester)-3,6,9,15-tetraaza-bicyclo[9.3.1]pentadeca-1(15),11,13-triene (PCTMB); 3,6,9-tris(**methylene phosphonic** acid)-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(13),11,13-triene (PCTMP); and N,N'-bis(**methylene phosphonic** acid)-2,11-**diaza**[3.3]-(2,6)**pyridinophane** (BP2P). The resp. aq. molar absorptivities are found to be 3424, 2513, and 3281/2210 M-1 cm-1. Fluorescence quantum efficiency is detd. against rhodamine 19 in basic ethanol and rhodamine 6G in ethanol. These values are 0.48, 0.21, and 0.40 for Tb-PCTMB, Tb-PCTMP, and Tb-BP2P, resp. Biodistribution studies performed in Sprague-Dawley rats indicate tissue site-selectivity. Fluorescence images of bone tissues are presented and demonstrate the potential for using the lanthanide chelates to perform site-directed in vivo imaging for the early identification of abnormal tissue.

L31 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:644464 HCAPLUS
DOCUMENT NUMBER: 126:13050
TITLE: Electrophotographic migration imaging member
INVENTOR(S): Malhotra, Shadi L.; Chen, Liqin; Perron, Marie-Eve
PATENT ASSIGNEE(S): Xerox Corp., USA
SOURCE: U.S., 144 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5563014	A	19961008	US 1995-442227	19950515
CA 2170298	AA	19961116	CA 1996-2170298	19960226
CA 2170298	C	20011002		
JP 08314241	A2	19961129	JP 1996-113457	19960508
BR 9602246	A	19980113	BR 1996-2246	19960514

PRIORITY APPLN. INFO.: US 1995-442227 A 19950515
OTHER SOURCE(S): MARPAT 126:13050

AB Disclosed is a migration imaging member comprising (a) a substrate, (b) a softenable layer comprising a softenable material and a photosensitive migration marking material, and (c) a transparentizing agent which transparentizes the migration marking material in contact therewith contained in at least one layer of the migration imaging member. Also disclosed is a process which comprises (1) providing a migration imaging member comprising (a) a substrate, (b) a softenable layer comprising a softenable material and a photosensitive migration marking material, and (c) a transparentizing agent which transparentizes the migration marking material in contact therewith contained in at least one layer of the migration imaging member, (2) uniformly charging the imaging member, (3) exposing the charged imaging member to an activating radiation at a wavelength to which the migration marking material is sensitive, and (4) causing the softenable material to soften and enabling a first portion of the migration marking material to migrate through the softenable material toward the substrate in an imagewise pattern while a second portion of the migration marking material remains substantially unmigrated within the softenable layer, wherein subsequent to migration of the first portion of migration marking material, either (a) the first portion of migration

marking material contacts the transparentizing agent and the second portion of migration marking material does not contact the transparentizing agent or (b) the second portion of migration marking material contacts the transparentizing agent and the first portion of migration marking material does not contact the transparentizing agent.

L31 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:333008 HCAPLUS
DOCUMENT NUMBER: 125:127644
TITLE: Method for obtaining improved image contrast in migration imaging members
INVENTOR(S): Limburg, William W.; Mammino, Joseph; Liebermann, George; Griffiths, Clifford H.; Shahin, Michael M.; Malhotra, Shadi L.; Chen, Liqin; Perron, Marie-Eve
PATENT ASSIGNEE(S): Xerox Corp., USA
SOURCE: U.S., 147 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5514505	A	19960507	US 1995-441360	19950515
CA 2169980	AA	19961116	CA 1996-2169980	19960221
CA 2169980	C	20010424		
JP 08314240	A2	19961129	JP 1996-113456	19960508
EP 743573	A2	19961120	EP 1996-303359	19960514
EP 743573	A3	19970305		
EP 743573	B1	20000906		
R: DE, FR, GB				

PRIORITY APPLN. INFO.: US 1995-441360 A 19950515
OTHER SOURCE(S): MARPAT 125:127644
AB Disclosed is a process which comprises (a) providing a migration imaging member comprising (1) a substrate and (2) a softenable layer comprising a softenable material and a photosensitive migration marking material present in the softenable layer as a monolayer of particles situated at or near the surface of the softenable layer spaced from the substrate, (b) uniformly charging the imaging member, (c) imagewise exposing the charged imaging member to activating radiation at a wavelength to which the migration marking material is sensitive, (d) causing the softenable material to soften and enabling a first portion of the migration marking material to migrate through the softenable material toward the substrate in an imagewise pattern while a second portion of the migration marking material remains substantially unmigrated within the softenable layer, and (e) contacting the second portion of the migration marking material with a transparentizing agent which transparentizes the migration marking material.

L31 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:795443 HCAPLUS
DOCUMENT NUMBER: 123:340399
TITLE: Method of selective fluorination
INVENTOR(S): Lal, Gauri S.
PATENT ASSIGNEE(S): Air Products and Chemicals, Inc., USA
SOURCE: U.S., 8 pp. Cont.-in-part of U.S. Ser. No. 187,422, abandoned.
CODEN: USXXAM

Kwon 10/088,884

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5442084	A	19950815	US 1994-330635	19941028
CA 2140610	AA	19950726	CA 1995-2140610	19950119
			US 1994-187422	19940125

PRIORITY APPLN. INFO.:
OTHER SOURCE(S): CASREACT 123:340399; MARPAT 123:340399

AB The present invention is a method for selectively fluorinating various **methylenephosphonate** and **methylenephosphorane** derivs. using an electrophilic fluorinating agent, such as N-fluoro-1,4-**diazabicyclo**[2.2.2]octane by fluorinating the monohalogenated **methylenephosphonate** or **methylenephosphorane** deriv. to produce **fluoromethylenephosphonate** or fluoro-**methylenephosphorane** derivs. useful as fluorinated Horner-Emmons or Wittig reagents in producing selectively fluorinated vinylic compds. Thus, reaction of di-Et (phenylsulfonyl)**methylenephosphonate** with NaH in THF followed by fluorination with SelectfluorTM in DMF gave 60% di-Et (phenylsulfonyl)**fluoromethylenephosphonate** along-with 15% di-Et (phenylsulfonyl)**difluoromethylenephosphonate**.

L31 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:364190 HCAPLUS
DOCUMENT NUMBER: 122:127701
TITLE: **Tricyclopolyazamacrocyclophosphonic** acids, complexes and derivatives thereof, for use as magnetic resonance contrast agents
INVENTOR(S): Kiefer, Garry E.
PATENT ASSIGNEE(S): Dow Chemical Co., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9426276	A1	19941124	WO 1994-US5071	19940506
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5385893	A	19950131	US 1993-58622	19930506
AU 9467849	A1	19941212	AU 1994-67849	19940506
AU 687400	B2	19980226		
EP 697872	A1	19960228	EP 1994-916043	19940506
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE				
HU 72649	A2	19960528	HU 1995-2023	19940506
CN 1125906	A	19960703	CN 1994-192528	19940506
FI 9505336	A	19951222	FI 1995-5336	19951106
NO 9504441	A	19960105	NO 1995-4441	19951106
LV 11429	B	19970420	LV 1995-361	19951206
			US 1993-58622	19930506
			WO 1994-US5071	19940506

PRIORITY APPLN. INFO.:

Search completed by David Schreiber. 308-4292

OTHER SOURCE(S): MARPAT 122:127701

AB Tri- and tetra-**cyclopolyazamacrocyclophosphonic** acid compds. and their derivs. are disclosed which may form inert complexes with Gd, Mn or Fe ions. The overall charge of the complex can be varied to alter the in vivo biolocalization. The complexes are useful as MRI contrast agents for diagnostic purposes. Prepn. of compds. of the invention, e.g. N,N'-bis(**methylenephosphonic** acid Et ester)-2,11-**diaza** [3.3](2,6)pydinophane is included, as are biodistribution data for 153Sm complexes of compds. of the invention.

L31 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:134700 HCAPLUS

DOCUMENT NUMBER: 120:134700

TITLE: Synthesis of aliphatic secondary **aminomethylenephosphonic** acids

AUTHOR(S): Long, Jiahong; Zi, Xueli; Li, Kangling; Li, Liangsi

CORPORATE SOURCE: Changsha Inst. Environ. Prot., Changsha, 410001, Peop. Rep. China

SOURCE: Huaxue Shiji (1993), 15(3), 182, 154
CODEN: HUSHDR; ISSN: 0258-3283

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

OTHER SOURCE(S): CASREACT 120:134700

AB Mannich reaction of H3PO3 with HCHO and RH (R = Et2N, 1,2,5,6-**tetrahydropyridin**-1-yl, piperidino) gave, after treatment with propylene oxide, 48-62.3% RCH2P(O)(OH)2.

L31 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1993:512424 HCAPLUS

DOCUMENT NUMBER: 119:112424

TITLE: **Bone** marrow transplantation in dogs after radioablation with a new holmium-166 amino phosphonic acid **bone**-seeking agent (**DOTMP**)

AUTHOR(S): Parks, N. J.; Kawakami, T. G.; Avila, M. J.; White, R.; Cain, G. R.; Raaka, S. D.; Hornoff, W.; Fisher, P.; Moore, P.; et al.

CORPORATE SOURCE: Inst. Toxicol. Environ. Health, Univ. California, Davis, CA, 95616, USA

SOURCE: Blood (1993), 82(1), 318-25
CODEN: BLOOAW; ISSN: 0006-4971

DOCUMENT TYPE: Journal

LANGUAGE: English

AB .beta.-Emitting 166Ho (t1/2 = 26.78 h, E(.beta.)max = 1.8 MeV) complexed with the phosphonic acid chelator, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid) (**DOTMP**) at a ligand-to-metal ratio of 1.5:1 binds to **bone**. This radioactive complex is a **bone** marrow-ablating radiopharmaceutical that appears useful for prepn. of **bone** marrow (BM) transplant recipients without the morbidity usually assocd. with total body irradn. preparatory regimens. In 7 splenectomized young adult beagle dogs, a 166Ho radiopharmaceutical dose of 370 MBq/kg body wt. provides an initial skeletal radioactivity burden of at least 1.5 GBq/kg skeleton and results in complete ablation of hematopoietic marrow cell populations within 7 days. The .beta.-particle flux distribution in BM-forming skeletal tissue is not uniform. Red marrow radiation doses varied 30-115 Gy as estd. by direct radioassay and autoradiog. analyses of both **bone** biopsies and postmortem samples; the median value of 61 Gy agreed with theor. expectations. The in vivo radioactivity distribution was evaluated with nuclear imaging methods. Apparently, normal hematopoiesis was restored in 3 dogs with

autologous BM transplants performed 5-6 days after administration of the marrow ablative radiopharmaceutical, 166Ho-**DOTMP**. BM biopsies at 7-10 mo posttransplantation indicate continued normal hematopoietic activity.

L31 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:574644 HCAPLUS
DOCUMENT NUMBER: 115:174644
TITLE: Radionuclide complexes as **bone** marrow suppressing agents
INVENTOR(S): Simon, Jaime; Garlich, Joseph R.; Wilson, David A.; McMillan, Kenneth
PATENT ASSIGNEE(S): Dow Chemical Co., USA
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 374501	A1	19900627	EP 1989-121564	19891121
EP 374501	B1	19930804		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL				
US 4882142	A	19891121	US 1988-284875	19881219
US 4976950	A	19901211	US 1989-435096	19891113
CA 2003326	AA	19900619	CA 1989-2003326	19891120
CA 2003326	C	19990119		
DK 8905827	A	19900620	DK 1989-5827	19891120
IL 92373	A1	19950831	IL 1989-92373	19891120
JP 02237936	A2	19900920	JP 1989-300943	19891121
JP 2795934	B2	19980910		
ZA 8908866	A	19910731	ZA 1989-8866	19891121
AT 92339	E	19930815	AT 1989-121564	19891121
AU 8945440	A1	19900621	AU 1989-45440	19891122
AU 625644	B2	19920716		
PRIORITY APPLN. INFO.:			US 1988-284875	19881219
			EP 1989-121564	19891121

AB **Bone** marrow is suppressed by the administration of 153Sm, 159Gd, 166Ho or 90Y complexes of aminophosphonic acid ligand(s) contg. the 1,4,7,10-tetraazacyclododecane moiety. A refluxing mixt. of 3.48 g 1,4,7,10-tetraazacyclodecane, 14 mL water, 17.2 mL conc. HCl and 7.2 g H3PO4 was treated with 13 g 37% HCHO, to give 1,4,7,10-tetraazacyclododecanetetramethylenephosphonic acid (**DOTMP**). This was treated with a 90YCl3 soln. in HCl, followed by pH adjustment to 7.5 (NaOH) to give 90Y-**DOTMP**. 90Y-**DOTMP** (1 mCi), injected i.v. into rats decreased the white blood cell count. The complexes may be used in the treatment of leukemia, lymphoma, myeloma, Hodgkin's disease, sickle cell anemia or thalassemia. The complexes may be used in conjunction with known chemotherapeutic agents.

L31 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:95158 HCAPLUS
DOCUMENT NUMBER: 114:95158
TITLE: Preparation of macrocyclic aminophosphonic acid complexes of radionuclides as neoplasm inhibitors
INVENTOR(S): Simon, Jaime; Wilson, David A.; Garlich, Joseph R.; Troutner, David E.

Kwon 10/088,884

PATENT ASSIGNEE(S): Dow Chemical Co., USA
SOURCE: Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 375376	A2	19900627	EP 1989-313308	19891219
EP 375376	A3	19910612		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 5059412	A	19911022	US 1988-284876	19881219
WO 9006776	A1	19900628	WO 1989-US5782	19891215
W: AU, BR, DK, FI, HU, JP, KR, NO				
RW: AT, BE, CH, DE, ES, FR, GB, IT, LU, NL, SE				
AU 9048282	A1	19900710	AU 1990-48282	19891215
AU 639899	B2	19930812		
EP 408701	A1	19910123	EP 1990-901464	19891215
EP 408701	B1	19941012		
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE				
BR 8907255	A	19910312	BR 1989-7255	19891215
HU 54897	A2	19910429	HU 1990-1163	19891215
HU 207454	B	19930428		
JP 03502936	T2	19910704	JP 1990-501907	19891215
ES 2061010	T3	19941201	ES 1990-901464	19891215
JP 2515929	B2	19960710	JP 1989-501907	19891215
CA 2005880	AA	19900619	CA 1989-2005880	19891218
CA 2005880	C	19990105		
IL 92784	A1	19940826	IL 1989-92784	19891218
AU 8947009	A1	19900621	AU 1989-47009	19891219
CN 1046739	A	19901107	CN 1989-109819	19891219
CN 1025983	B	19940928		
ZA 8909734	A	19910828	ZA 1989-9734	19891219
DK 9001959	A	19900816	DK 1990-1959	19900816
NO 9003632	A	19901017	NO 1990-3632	19900817
NO 180434	B	19970113		
NO 180434	C	19970423		
AU 9350685	A1	19940224	AU 1993-50685	19931112
AU 657641	B2	19950316		

PRIORITY APPLN. INFO.:

US 1988-284876	A	19881219
US 1984-616985	B2	19840604
US 1985-738010	B2	19850528
US 1985-803376	B2	19851204
US 1987-50263	A2	19870514
WO 1989-US5782	A	19891215

OTHER SOURCE(S): MARPAT 114:95158

AB 153Sm, 159Gd, 166Ho, 177Lu, 90Y or 175Yb are complexes with macrocyclic aminophosphonic acids contg. the 1,4,7,10-tetraazacyclododecane moiety and having the N and P interconnected by (un)substituted alkylene. The complexes are useful in the treatment of **bone**-metastatic cancer.

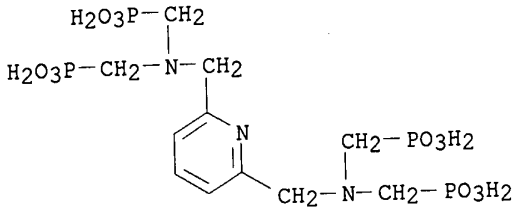
A refluxing mixt. of 3.48 g 1,4,7,10-tetraazacyclododecane, 17.2 mL conc. HCl, 7.2 g H3PO4 and 14 mL water was treated with 13 g HCHO, to give 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylphosphonic acid (**DOTMP**). This was complexed with 166Ho at pH 7-8, to give **DOTMP**-166Ho. Biodistribution studies of **DOTMP**-166Ho in rats showed strong accumulation in the **bone**.

Search completed by David Schreiber, 308-4292

L31 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1974:446884 HCAPLUS
DOCUMENT NUMBER: 81:46884
TITLE: Conformational transitions in glycogen phosphorylase reported by covalently bound pyridoxamine derivatives
AUTHOR(S): Feldmann, Knut; Gaugler, Bernhard J. M.; Winkler, Heinz; Helmreich, Ernst J. M.
CORPORATE SOURCE: Sch. Med., Univ. Wuerzburg, Wuerzburg, Fed. Rep. Ger.
SOURCE: Biochemistry (1974), 13(10), 2222-30
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB NaBH4-reduced rabbit skeletal muscle phosphorylases b and a dissoc. on acidification completely to monomers. The conformational change leading to the disruption of the interprotomeric bonds is reported by the absorbance and fluorescence of the bound pyridoxamine 5'-phosphate and analogs modified at the 5' position. The structural alteration was shown to involve changes in dimer conformations followed by monomerization. A comparison of the responses to pH of several reduced phosphorylase derivs. carrying the pyridoxamine, the 5'-**deoxypyridoxaminemethylenephosphonate**, and the pyridoxamine 5'-monomethyl ester analogs indicated that the ionization of the 5' group is not related to the structural change. Neutralization (or 5'-AMP addn.) completely reversed the pH perturbation of reduced phosphorylases resulting in reassocn. of monomers to oligomers and in reactivation, the rate of which was enhanced by substrates. 5'-AMP and substrates also protected against inactivation by acidification. But, in the absence of 5'-AMP, substrates alone were ineffective. The absorbance and fluorescence intensity of reduced phosphorylase b at a given pH (6.25) was concn. dependent whereas the quantum yield was independent of concn. This together with the change of the fluorescence intensity of glutardialdehyde crosslinked reduced dimer b with pH change indicated that the spectral properties, including the fluorescence polarization, of bound pyridoxamine 5'-phosphate are the same in the monomer and in at least one of the dimeric forms. This makes it unlikely that the chromophore is buried between the 2 subunits and can only be exposed on dissocn. The spectral properties of the cofactor in oligomeric reduced phosphorylases b and a at neutral pH can be explained without assuming that the chromophore is completely immersed in a hydrophobic crevasse. The structure of the binding site must only enable the 3'-OH group of the cofactor be be H-bonded. There is no convincing reason why other protonatable groups, esp. the 5'-phosphate moiety could not react in a more hydrophilic environment.

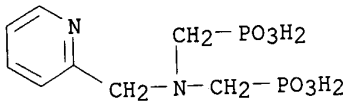
L2 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 335373-45-0 REGISTRY
CN Phosphonic acid, [2,6-pyridinediylbis[methylenenitrilobis(methylene)]]tetr
akis- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C11 H23 N3 O12 P4
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

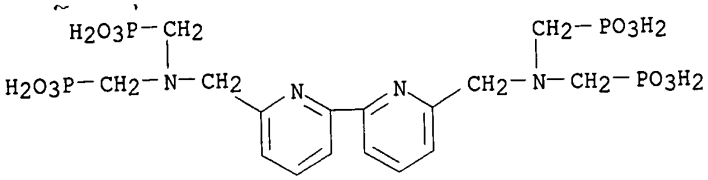
L2 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 193003-47-3 REGISTRY
CN Phosphonic acid, [[(2-pyridinylmethyl)imino]bis(methylene)]bis- (9CI) (CA
INDEX NAME)
FS 3D CONCORD
MF C8 H14 N2 O6 P2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 147974-57-0 REGISTRY
CN Phosphonic acid, [[2,2'-bipyridine]-6,6'-diylbis(methylenedinitrilo)]tetra
kis- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C16 H26 N4 O12 P4
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=>
Uploading pctmp.str

L3 STRUCTURE UPLOADED

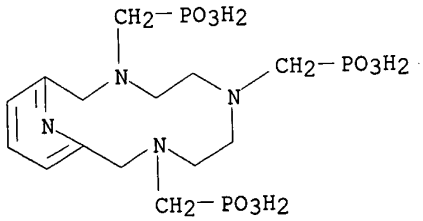
=> s l3 full
FULL SEARCH INITIATED 18:41:51 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 222 TO ITERATE

100.0% PROCESSED 222 ITERATIONS 4 ANSWERS
SEARCH TIME: 00.00.01

L4 4 SEA SSS FUL L3

=> d l4 1-4

L4 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 211321-07-2 REGISTRY
CN Phosphonic acid, [3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triyltris(methylene)]tris-, tetrahydrochloride (9CI) (CA INDEX NAME)
MF C14 H27 N4 O9 P3 . 4 Cl H
SR CA
LC STN Files: CA, CAPLUS
CRN (150375-17-0)

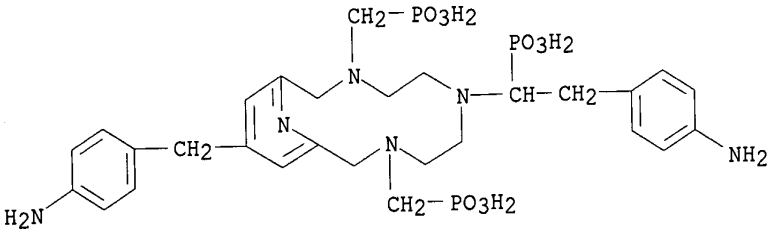


●4 HCl

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L4 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 153754-54-2 REGISTRY

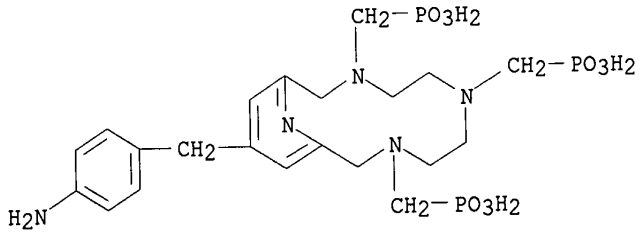
CN Phosphonic acid, [[13-[(4-aminophenyl)methyl]-6-[2-(4-aminophenyl)-1-phosphonoethyl]-3,6,9,15-tetraazapentacyclo[9.3.1]pentadeca-1(15),11,13-triene-3,9-diyl]bis(methylene)]bis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,6,9,15-Tetraazabicyclo[9.3.1]pentadecane, phosphonic acid deriv.
FS 3D CONCORD
MF C28 H41 N6 O9 P3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L4 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 153754-53-1 REGISTRY
CN Phosphonic acid, [[13-[(4-aminophenyl)methyl]-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triyl]tris(methylene)]tris- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,6,9,15-Tetraazabicyclo[9.3.1]pentadecane, phosphonic acid deriv.
FS 3D CONCORD
MF C21 H34 N5 O9 P3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

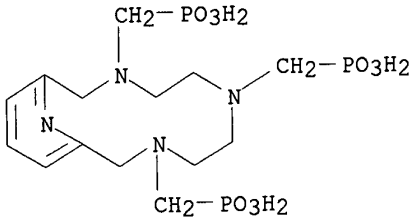


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L4 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2003 ACS
RN 150375-17-0 REGISTRY
CN Phosphonic acid, [3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triyltris(methylene)]tris- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,6,9,15-Tetraazabicyclo[9.3.1]pentadecane, phosphonic acid deriv.

FS 3D CONCORD
MF C14 H27 N4 O9 P3
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL

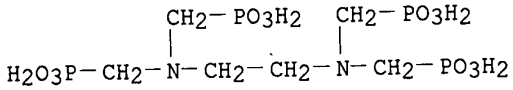


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
11 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=>

L20 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **1429-50-1** REGISTRY
CN Phosphonic acid, [1,2-ethanediylbis[nitrilobis(methylene)]]tetrakis- (9CI)
(CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [ethylenebis(nitrilodimethylene)]tetra- (6CI, 7CI, 8CI)
OTHER NAMES:
CN Cublen 3115
CN Dequest 2040
CN Dequest 2041
CN Editempa
CN EDPA
CN EDPA (chelating agent)
CN EDTF
CN EDTMP
CN EDTMPA
CN EDTPA
CN EDTPH
CN Ethylenedi(nitrilodimethylene)tetraphosphonic acid
CN Ethylenediamine-N,N,N',N'-tetra(methylphosphonic acid)
CN Ethylenediamine-N,N,N',N'-tetrakis(methylenephosphonic acid)
CN Ethylenediaminetetra(methylenephosphonic acid)
CN Ethylenediaminetetrakis(methylenephosphonic acid)
CN Ethylenediaminetetrakis(methylphosphonic acid)
CN Ethylenediaminotetra(methylenephosphonic acid)
CN N,N,N',N'-Tetrakis(phosphonomethyl)ethylenediamine
CN Wayplex 45K
CN [Ethylenebis(nitrilodimethylene)]tetraphosphonic acid
FS 3D CONCORD
DR 54579-31-6, 66300-26-3, 85497-53-6, 244775-21-1
MF C6 H20 N2 O12 P4
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST,
CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB,
MEDLINE, MSDS-OHS, NIOSHTIC, PIRA, SPECINFO, TOXCENTER, USPAT2,
USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



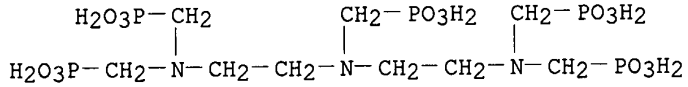
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1076 REFERENCES IN FILE CA (1957 TO DATE)
192 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1081 REFERENCES IN FILE CAPLUS (1957 TO DATE)
5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s 15827-60-8/rn
L21 1 15827-60-8/RN

=> d

L21 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **15827-60-8** REGISTRY
CN Phosphonic acid, [[(phosphonomethyl)imino]bis[2,1-ethanediylnitrilobis(methylene)]]tetrakis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [[bis[2-[bis(phosphonomethyl)amino]ethyl]amino]methyl]- (8CI)
OTHER NAMES:
CN CIX
CN Cublen D 50
CN Dequest 2060
CN Dequest 2060S
CN DETPMP
CN Diethylenetriamine-N,N,N',N'',N''-penta(methylenephosphonic acid)
CN Diethylenetriamine-N,N,N',N'',N''-pentakis(methylenephosphonic acid)
CN Diethylenetriaminepenta(methylenephosphonic acid)
CN Diethylenetriaminepentakis(methylenephosphonic acid)
CN Diethylenetriaminepentakis(methylphosphonic acid)
CN Diethylenetriaminopenta(methylenephosphonic acid)
CN DQ 2060
CN DTPF
CN DTPMP
CN DTPP
CN DTPPA
CN Ethylenetriaminepenta(methylenephosphonic acid)
CN Lonza 905
CN Sequion 40H50
CN Versenate PS
FS 3D CONCORD
DR 67774-91-8, 244775-22-2, 291513-72-9
MF C9 H28 N3 O15 P5
CI COM
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, GMELIN*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MSDS-OHS, PIRA, PROMT, TOXCENTER, ULIDAT, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

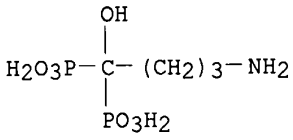
781 REFERENCES IN FILE CA (1957 TO DATE)
91 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
782 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> s 66376-36-1/rn
L22 1 66376-36-1/RN

=> d

L22 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **66376-36-1** REGISTRY

CN Phosphonic acid, (4-amino-1-hydroxybutylidene)bis- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 4-Amino-1-hydroxybutane-1,1-diphosphonate
CN 4-Amino-1-hydroxybutane-1,1-diphosphonic acid
CN 4-Amino-1-hydroxybutane-1,1-diyldiphosphonic acid
CN 4-Amino-1-hydroxybutylidene-1,1-bis(phosphonic acid)
CN ABDP
CN Alendronate
CN Alendronic acid
FS 3D CONCORD
MF C4 H13 N O7 P2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



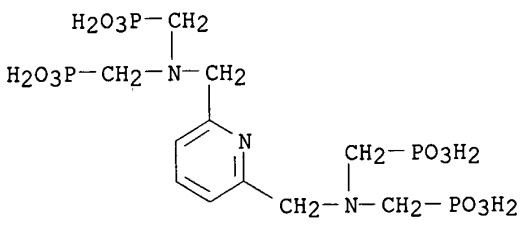
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

738 REFERENCES IN FILE CA (1957 TO DATE)
32 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
738 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> s 335373-45-0/rn or 13598-36-2/rn
1 335373-45-0/RN
1 13598-36-2/RN
L23 2 335373-45-0/RN OR 13598-36-2/RN

=> d

L23 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN **335373-45-0** REGISTRY
CN Phosphonic acid, [2,6-pyridinediylbis[methylenenitrilobis(methylene)]]tetrakis- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C11 H23 N3 O12 P4
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

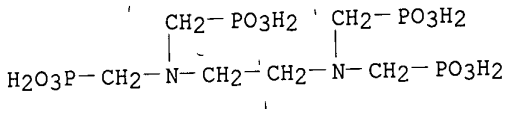
1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> d l23 2

L23 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN **13598-36-2** REGISTRY
CN Phosphonic acid (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN Dihydroxyphosphine oxide
CN Phosphorous acid
MF H3 O3 P
CI COM
LC STN Files: AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DETHERM*, DIPPR*, EMBASE, IFICDB, IFIPAT, IFIUDB, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, TOXCENTER, TULSA, USPAT2, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** FRAGMENT DIAGRAM IS INCOMPLETE ***
5943 REFERENCES IN FILE CA (1957 TO DATE)
3002 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5950 REFERENCES IN FILE CAPLUS (1957 TO DATE)
8 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

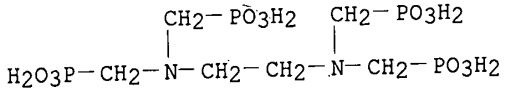
L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 29462-95-1 REGISTRY
CN Phosphonic acid, [1,2-ethanediylbis[nitrilobis(methylene)]]tetrakis-, trisodium salt (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [ethylenebis(nitrilodimethylene)]tetra-, trisodium salt (8CI)
OTHER NAMES:
CN **Trisodium ethylenediaminetetramethylenephosphonate**
MF C6 H20 N2 O12 P4 . 3 Na
LC STN Files: CA, CAPLUS, CHEMCATS, CHEMLIST, IFICDB, IFIPAT, IFIUDB, TOXCENTER, USPATFULL
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (1429-50-1)



●3 Na

6 REFERENCES IN FILE CA (1957 TO DATE)
6 REFERENCES IN FILE CAPLUS (1957 TO DATE)

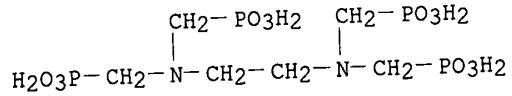
L6 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 1429-50-1 REGISTRY
CN Phosphonic acid, [1,2-ethanediylbis[nitrilobis(methylene)]]tetrakis- (9CI)
(CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [ethylenebis(nitrilodimethylene)]tetra- (6CI, 7CI, 8CI)
OTHER NAMES:
CN Cublen 3115
CN Dequest 2040
CN Dequest 2041
CN **Editempa**
CN EDPA
CN EDPA (chelating agent)
CN EDTF
CN EDTMP
CN EDTMPA
CN EDTPA
CN EDTPH
CN Ethylenedi(nitrilodimethylene)tetraphosphonic acid
CN Ethylenediamine-N,N,N',N'-tetra(methylphosphonic acid)
CN Ethylenediamine-N,N,N',N'-tetrakis(methylenephosphonic acid)
CN Ethylenediaminetetra(methylenephosphonic acid)
CN Ethylenediaminetetrakis(methylenephosphonic acid)
CN Ethylenediaminetetrakis(methylphosphonic acid)
CN Ethylenediaminotetra(methylenephosphonic acid)
CN N,N,N',N'-Tetrakis(phosphonomethyl)ethylenediamine
CN Wayplex 45K
CN [Ethylenebis(nitrilodimethylene)]tetraphosphonic acid
FS 3D CONCORD
DR 54579-31-6, 66300-26-3, 85497-53-6, 244775-21-1
MF C6 H20 N2 O12 P4
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MSDS-OHS, NIOSHTIC, PIRA, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1078 REFERENCES IN FILE CA (1957 TO DATE)
192 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1083 REFERENCES IN FILE CAPLUS (1957 TO DATE)
5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

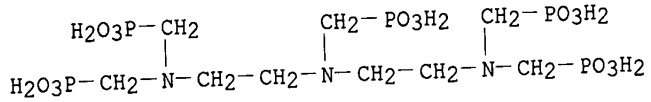
L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 1429-50-1 REGISTRY
CN Phosphonic acid, [1,2-ethanediylbis[nitrilobis(methylene)]]tetrakis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [ethylenebis(nitrilodimethylene)]tetra- (6CI, 7CI, 8CI)
OTHER NAMES:
CN Cublen 3115
CN Dequest 2040
CN Dequest 2041
CN Editempa
CN EDPA
CN EDPA (chelating agent)
CN EDTF
CN **EDTMP**
CN EDTMPA
CN EDTPA
CN EDTPH
CN Ethylenedi(nitrilodimethylene)tetraphosphonic acid
CN Ethylenediamine-N,N,N',N'-tetra(methylphosphonic acid)
CN Ethylenediamine-N,N,N',N'-tetrakis(methylenephosphonic acid)
CN Ethylenediaminetetra(methylenephosphonic acid)
CN Ethylenediaminetetrakis(methylenephosphonic acid)
CN Ethylenediaminetetrakis(methylphosphonic acid)
CN Ethylenediaminotetra(methylenephosphonic acid)
CN N,N,N',N'-Tetrakis(phosphonomethyl)ethylenediamine
CN Wayplex 45K
CN [Ethylenebis(nitrilodimethylene)]tetraphosphonic acid
FS 3D CONCORD
DR 54579-31-6, 66300-26-3, 85497-53-6, 244775-21-1
MF C6 H20 N2 O12 P4
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MSDS-OHS, NIOSHTIC, PIRA, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1078 REFERENCES IN FILE CA (1957 TO DATE)
192 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1083 REFERENCES IN FILE CAPLUS (1957 TO DATE)
5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

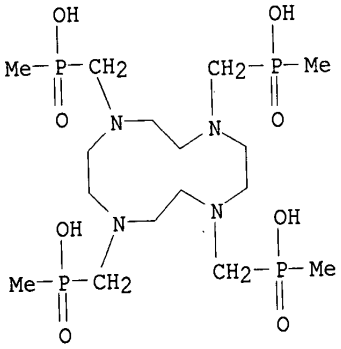
L8 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 15827-60-8 REGISTRY
CN Phosphonic acid, [[(phosphonomethyl)imino]bis[2,1-ethanediylnitrilobis(methylene)]]tetrakis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [[bis[2-[bis(phosphonomethyl)amino]ethyl]amino]methyl]- (8CI)
OTHER NAMES:
CN CIX
CN Cublen D 50
CN Dequest 2060
CN Dequest 2060S
CN DETPMP
CN Diethylenetriamine-N,N,N',N'',N''-penta(methylenephosphonic acid)
CN Diethylenetriamine-N,N,N',N'',N''-pentakis(methylenephosphonic acid)
CN Diethylenetriaminepenta(methylenephosphonic acid)
CN Diethylenetriaminepentakis(methylenephosphonic acid)
CN Diethylenetriaminepentakis(methylphosphonic acid)
CN Diethylenetriaminopenta(methylenephosphonic acid)
CN DQ 2060
CN DTPF
CN **DTPMP**
CN DTPP
CN DTPPA
CN Ethylenetriaminepenta(methylenephosphonic acid)
CN Lonza 905
CN Sequion 40H50
CN Versenate PS
FS 3D CONCORD
DR 67774-91-8, 244775-22-2, 291513-72-9
MF C9 H28 N3 O15 P5
CI COM
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, GMELIN*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MSDS-OHS, PIRA, PROMT, TOXCENTER, ULIDAT, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

784 REFERENCES IN FILE CA (1957 TO DATE)
91 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
785 REFERENCES IN FILE CAPLUS (1957 TO DATE)

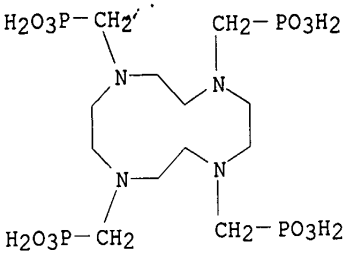
L9 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 132446-35-6 REGISTRY
CN Phosphinic acid, [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayltetrakis(methylene)]tetrakis[methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10-Tetraazacyclododecane, phosphinic acid deriv.
OTHER NAMES:
CN **DOTMP**
FS 3D CONCORD
MF C16 H40 N4 O8 P4
CI COM
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CHEMINFORMRX, CIN, PROMT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

13 REFERENCES IN FILE CA (1957 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
13 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L9 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 91987-74-5 REGISTRY
CN Phosphonic acid, [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayltetrakis(methylene)]tetrakis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10-Tetraazacyclododecane, phosphonic acid deriv.
OTHER NAMES:
CN 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrakis(methylenephosphonic acid)
CN 1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetramethylenephosphonic acid
CN **DOTMP**
CN DOTP
CN N,N',N'',N'''-Tetrakis(phosphonomethyl)-1,4,7,10-tetraazacyclododecane
FS 3D CONCORD
MF C12 H32 N4 O12 P4
CI COM
LC STN Files: BEILSTEIN*, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CIN, GMELIN*, MEDLINE, PROMT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

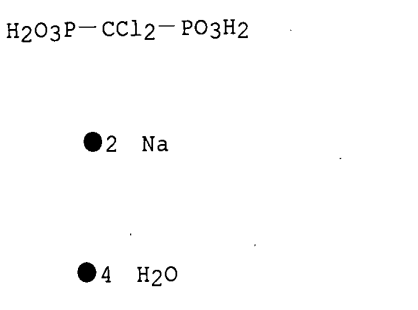


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

52 REFERENCES IN FILE CA (1957 TO DATE)
29 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
52 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=>

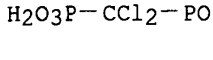
L1 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 88416-50-6 REGISTRY
CN Phosphonic acid, (dichloromethylene)bis-, disodium salt, tetrahydrate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Disodium clodronate tetrahydrate**
MF C H4 Cl2 O6 P2 . 4 H2 O . 2 Na
LC STN Files: BIOSIS, CA, CAPLUS, MRCK*
(*File contains numerically searchable property data)
CRN (10596-23-3)



5 REFERENCES IN FILE CA (1957 TO DATE)
5 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 22560-50-5 REGISTRY
CN Phosphonic acid, (dichloromethylene)bis-, disodium salt (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, (dichloromethylene)di-, disodium salt (8CI)
OTHER NAMES:
CN (Dichloromethylene)diphosphonate disodium
CN BM 06011
CN Bonefos
CN Clasteon
CN **Clodronate disodium salt**
CN **Clodronate sodium**
CN Clodronic acid disodium salt
CN DClMDP
CN Dichloromethylenebisphosphonic acid disodium salt
CN Dichloromethylenediphosphonic acid disodium salt
CN Difoafonal
CN Diphosfonal
CN Disodium (dichloromethane)diphosphonate
CN Disodium (dichloromethylene)diphosphonate
CN **disodium clodronate**
CN Lodronate
CN Loron
CN Mebonat
CN Ossiten
CN Ostac
CN Sodium (dichloromethylene)diphosphonate
CN **Sodium clodronate**
MF C H4 Cl2 O6 P2 . 2 Na
LC STN Files: ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CHEMCATS, CHEMLIST, CSCHEM, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PROMT, RTECS*, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)

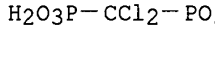
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (10596-23-3)



●2 Na

97 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
97 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 10596-24-4 REGISTRY
CN Phosphonic acid, (dichloromethylene)bis-, tetrasodium salt (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, (dichloromethylene)di-, tetrasodium salt (8CI)
OTHER NAMES:
CN **Tetrasodium clodronate**
CN Tetrasodium dichloromethylenebis(phosphonate)
MF C H4 Cl2 O6 P2 . 4 Na
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, USPATFULL
(*File contains numerically searchable property data)
CRN (10596-23-3)

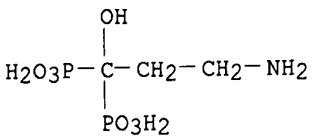


●4 Na

5 REFERENCES IN FILE CA (1957 TO DATE)
5 REFERENCES IN FILE CAPLUS (1957 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> d l2 1-2

L2 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 109552-15-0 REGISTRY
CN Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt, pentahydrate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Disodium pamidronate pentahydrate**
MF C3 H11 N O7 P2 . 5 H2 O . 2 Na
SR US Adopted Names Council
LC STN Files: ADISINSIGHT, ANABSTR, BIOSIS, CA, CAPLUS, CBNB, DRUGPAT, DRUGUPDATES, IPA, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
CRN (40391-99-9)

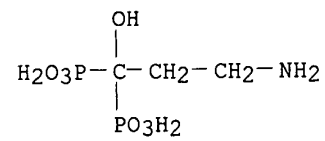


● 2 Na

● 5 H_2O

4 REFERENCES IN FILE CA (1957 TO DATE)
4 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS
RN 57248-88-1 REGISTRY
CN Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3-Amino-1-hydroxypropane-1,1-diphosphonic acid disodium salt
CN Aminomux
CN APD
CN Aredia
CN CGP 23339A
CN CGP 23339AE
CN Disodium 3-amino-1-hydroxypropane-1,1-diphosphonate
CN **Disodium pamidronate**
CN **Pamidronate disodium**
CN Pamidronic acid disodium salt
MF C3 H11 N O7 P2 . 2 Na
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DIOGENES, DRUGPAT, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (40391-99-9)



2 Na

101 REFERENCES IN FILE CA (1957 TO DATE)
102 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L28 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:444931 CAPLUS
DOCUMENT NUMBER: 138:69067
TITLE: 177Lu-labeled cyclic polyaminophosphonates as potential agents for **bone** pain palliation
AUTHOR(S): Das, Tapas; Chakraborty, Sudipta; Unni, P. R.; Banerjee, Sharmila; Samuel, Grace; Sarma, H. D.; Venkatesh, Meera; Pillai, M. R. A.
CORPORATE SOURCE: Radiopharmaceuticals Division, Bhabha Atomic Research Centre, Mumbai, 400 085, India
SOURCE: Applied Radiation and Isotopes (2002), 57(2), 177-184
CODEN: ARISEF; ISSN: 0969-8043
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 177Lu (T1/2=6.71 d, E.beta.(max)=497 keV) has radionuclidic properties suitable for use in palliative therapy of **bone** pain due to metastasis. 177Lu was produced in high-specific activity (3-4 TBq/g) and excellent radionuclidic purity (100%) by thermal neutron bombardment of natural Lu target. Two cyclic tetraaminomethylene phosphonate ligands, namely DOTMP and CTMP were synthesized and radiolabeled with 177Lu. The 177Lu-DOTMP complex was formed with very high yield (>99%) and showed excellent stability (up to 40 d at room temp.). Biodistribution of 177Lu-DOTMP was carried out in Wistar rats and the complex showed significant **bone** uptake (4.23%/g in femur and 5.23% in tibia at 3 h p. i.), rapid clearance from blood (no activity at 3 h p. i.) and min. uptake in soft tissues.

IT Pharmacokinetics
(**bone** uptake; 177Lu-labeled cyclic polyaminophosphonates as potential agents for **bone** pain palliation)

IT **Bone**, neoplasm
(metastasis; 177Lu-labeled cyclic polyaminophosphonates as potential agents for **bone** pain palliation)

IT Pain
Radiopharmaceuticals
(177Lu-labeled cyclic polyaminophosphonates as potential agents for **bone** pain palliation)

IT 13598-36-2, Phosphonic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(anhyd.; 177Lu-labeled cyclic polyaminophosphonates as potential agents for **bone** pain palliation)

IT 480439-82-5P 480439-83-6P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(177Lu-labeled cyclic polyaminophosphonates as potential agents for **bone** pain palliation)

IT **91987-74-5P**, DOTMP 107446-90-2P
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(177Lu-labeled cyclic polyaminophosphonates as potential agents for **bone** pain palliation)

IT 294-90-6, Cyclen 295-37-4, Cyclam
RL: RCT (Reactant); RACT (Reactant or reagent)
(177Lu-labeled cyclic polyaminophosphonates as potential agents for **bone** pain palliation)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 10 OF 19 USPATFULL

ACCESSION NUMBER:	1999:56497 USPATFULL
TITLE:	Composition and method for the palliation of pain associated with diseases of the **bone** and **bone** joints
INVENTOR(S):	Jia, Wei, Columbia, MO, United States
PATENT ASSIGNEE(S):	Mitreoak, Ltd., Columbia, MO, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5902825		19990511	
APPLICATION INFO.:	US 1997-779719		19970107	(8)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Nazario-Gonzalez, Porfirio
LEGAL REPRESENTATIVE:	Shook, Hardy & Bacon LLP
NUMBER OF CLAIMS:	30
EXEMPLARY CLAIM:	1,10
LINE COUNT:	717

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A therapeutic composition and method of using the same for the palliation or relief of pain in patients having diseases which affect the **bone** and **bone** joints including metastatic **bone** cancer, arthritis, and other inflammatory arthropathies. The therapeutic composition comprises as the active agent a complex formed of non-radioactive metal ions and organic phosphonic acid ligands, or pharmaceutically acceptable salts thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT Analgesics
IT Arthritis
IT Bone diseases
IT Bone tumors
IT Joint (anatomical)
(non-radioactive metal ion complexes with phosphonates for the palliation of pain assocd. with diseases of the bone and bone joints)
IT 1429-50-1DP, Sn(IV) complexes 210417-02-0P
(non-radioactive metal ion complexes with phosphonates for the palliation of pain assocd. with diseases of the bone and bone joints)
IT 1429-50-1D, Edtmp, metal complexes 1984-15-2D, Methylenediphosphonic acid, metal complexes 2809-21-4D, Ehdp, metal complexes 6419-19-8D, NTP, metal complexes 7440-19-9D, Samarium, complexes with phosphonates 7440-31-5D, Tin, complexes with phosphonates 7440-45-1D, Cerium, complexes with phosphonates 7440-55-3D, Gallium, complexes with phosphonates 7440-74-6D, Indium, complexes with phosphonates 15049-85-1D, Aedp, metal complexes 15827-60-8D, Dtpmp, metal complexes 22537-33-3, Ga3+, biological studies **91987-74-5D**, Sn(IV) complexes **91987-74-5D**, metal complexes
(non-radioactive metal ion complexes with phosphonates for the palliation of pain assocd. with diseases of the bone and bone joints)

L28 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:200426 CAPLUS
DOCUMENT NUMBER: 120:200426
TITLE: Targeted delivery of growth factors for **bone** regeneration
INVENTOR(S): Garlich, Joseph R.; Lynch, Samuel E.; Pribish, James R.
PATENT ASSIGNEE(S): Dow Chemical Co., USA; Institute of Molecular Biology, Inc.
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9400145	A1	19940106	WO 1993-US6254	19930630
W: AU, CA, FI, HU, JP, KR, NO, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5505931	A	19960409	US 1993-26800	19930304
AU 9346600	A1	19940124	AU 1993-46600	19930630
CN 1092076	A	19940914	CN 1993-109549	19930630
JP 07508979	T2	19951005	JP 1993-502666	19930630
HU 71220	A2	19951128	HU 1994-3840	19930630
WO 9420487	A1	19940915	WO 1994-US130	19940104
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2157402	AA	19940915	CA 1994-2157402	19940104
AU 9460204	A1	19940926	AU 1994-60204	19940104
EP 687261	A1	19951220	EP 1994-906519	19940104
R: BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE				
JP 08507517	T2	19960813	JP 1994-519955	19940104
FI 9406156	A	19950227	FI 1994-6156	19941229
NO 9405093	A	19950227	NO 1994-5093	19941230

PRIORITY APPLN. INFO.:		
	US 1992-906980	19920630
	US 1993-26800	19930304
	WO 1993-US6254	19930630
	WO 1994-US130	19940104

AB A target delivery compn., esp. suitable for site delivery to **bone**, comprises growth factors linked, optionally using an acid cleavable linker, to a polyaminomethylenephosphonic acid ligand. The compn. is activated for the growth factors at the **bone** site, but it remains inactive while circulating in the body. For example, insulin-like growth factor was treated with 4-isothiocyanatophthalic anhydride and N-[1-(4-aminobenzyl)-N,N'-ethylenediamine]-N',N''-ethylenediamine-N,N,N',N''-pentamethylenephosphonic acid to give a conjugate, which was labeled with 125I and injected to rats to show uptake of the conjugate by **bone**.

IT **Bone**
(regeneration of, by targeted delivery of growth factor conjugates)

IT Animal growth regulators
RL: BIOL (Biological study)
(blood platelet-derived growth factors, conjugates, with polyaminomethylenephosphonates, targeted delivery of, for **bone** regeneration)

IT Animal growth regulators
RL: BIOL (Biological study)
(cartilage-inducing factors, conjugates, with polyaminomethylenephosphonates, targeted delivery of, for **bone** regeneration)

IT **Bone**, disease
(demineralization, prevention of, by targeted delivery of growth factor conjugates)
IT Animal growth regulators
RL: BIOL (Biological study)
(osteogenins, conjugates, with polyaminomethylenephosphonates, targeted delivery of, for **bone** regeneration)
IT Animal growth regulators
RL: BIOL (Biological study)
(transforming growth factors, conjugates, with polyaminomethylenephosphonates, targeted delivery of, for **bone** regeneration)
IT 294-90-6, 1,4,7,10-Tetraazacyclododecane 295-37-4, 1,4,8,11-Tetraazacyclotetradecane 143944-04-1 143944-07-4 **150375-17-0** 153754-47-3 153754-48-4 153754-49-5 153754-50-8 153754-51-9 153754-52-0 153754-53-1 153754-54-2
RL: BIOL (Biological study)
(as ligand in prepn. of growth factor conjugates for targeted delivery for **bone** regeneration)
IT 104851-97-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(catalytic redn. of)
IT 66753-48-8P, 4-Isothiocyanatophthalic acid
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and conversion of, to anhydride)
IT 153754-36-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and hydrolysis of)
IT 153754-56-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, with formaldehyde)
IT 153754-44-0P 153754-58-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, with phosphorous acid and formaldehyde)
IT 153754-40-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, with thiophosgene)
IT 153754-37-1P 153754-39-3P 153754-42-8P 153754-45-1P 153754-57-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and redn. of)
IT 55629-02-2P 139451-47-1P 143944-05-2P 143944-06-3P 153754-38-2P 153754-41-7P 153754-43-9P 153754-46-2P
RL: PREP (Preparation)
(prepn. of, as ligand in prepn. of growth factor conjugates for targeted delivery to **bone**)
IT 153754-59-7P, 4-Isothiocyanatophthalic anhydride
RL: PREP (Preparation)
(prepn. of, as linker in prepn. of growth factor conjugates for targeted delivery to **bone**)
IT 463-71-8, Thiophosgene
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with (aminobenzyl)diethylenetriaminepentamethylenephosphonic acid)
IT 50-00-0, Formaldehyde, reactions 13598-36-2, Phosphorous acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with (nitrobenzyl)diethylenetriamine)
IT 5339-26-4, p-Nitrophenethyl bromide

RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with ethylenediamine)
IT 107-15-3, 1,2-Ethanediamine, reactions 111-40-0, Diethylenetriamine
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with nitrophenethyl bromide)
IT 153754-35-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with phosphite and paraformaldehyde)
IT 124266-39-3 153754-55-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with phosphorous acid)
IT 124888-28-4 125767-61-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with phosphorous acid and formalin)
IT 122-52-1, Triethyl phosphite
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with tetraazacyclododecane and paraformaldehyde)
IT 30525-89-4, Paraformaldehyde
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with tetraazacyclododecane and tri-Et phosphite)
IT 5434-21-9, 4-Aminophthalic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with thiophosgene)
IT 9061-61-4D, Nerve growth factor, conjugates with polyaminomethylenephosphonates 61912-98-9D, Insulin-like growth factor, conjugates with polyaminomethylenephosphonates 62031-54-3D, Fibroblast growth factor, conjugates with polyaminomethylenephosphonates 62229-50-9D, Epidermal growth factor, conjugates with polyaminomethylenephosphonates 67763-96-6D, Insulin-like growth factor 1, conjugates with polyaminomethylenephosphonates 67763-97-7D, Insulin-like growth factor 2, conjugates with polyaminomethylenephosphonates
RL: BIOL (Biological study)
(targeted delivery of, for **bone** regeneration)

L28 ANSWER 18 OF 19 USPATFULL
ACCESSION NUMBER: 90:94884 USPATFULL
TITLE: **Bone** marrow suppressing agents
INVENTOR(S): Simon, Jaime, Angleton, TX, United States
Garlich, Joseph R., Lake Jackson, TX, United States
Wilson, David A., Richwood, TX, United States
McMillan, Kenneth, Richwood, TX, United States
PATENT ASSIGNEE(S): The Dow Chemical Company, Midland, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4976950		19901211
APPLICATION INFO.:	US 1989-435096		19891113 (7)

DISCLAIMER DATE: 20061121
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1988-284875, filed on 19 Dec 1988, now patented, Pat. No. US 4882142, issued on 21 Nov 1989
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Maples, John S.
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 782
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention concerns a method for suppressing **bone** marrow which comprises administering to a mammal at least one **bone**

marrow suppressing complex of a radionuclide selected from the group consisting of Samarium-153, Gadolinium-159, Holmium-166 and Yttrium-90 and at least one macrocyclic aminophosphonic acid ligand containing the 1,4,7,10-tetraazacyclododecane moiety, or a physiologically acceptable salt thereof. Suitable compositions for use in this method are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT Bone marrow
(suppression of, with radionuclide complexes of tetraazacyclododecanetetramethylenephosphonic acid, in treatment of cancer and genetic diseases)

IT Neoplasm inhibitors
(Hodgkin's disease, radionuclide complexes of tetraazacyclododecanetetramethylephosphonic acid)

IT Radioelements, compounds
(complexes, with tetraazacyclododecanetetramethylenephosphonic acid, in treatment of cancer and genetic diseases)

IT Neoplasm inhibitors
(leukemia, radionuclide complexes of tetraazacyclododecanetetramethylephosphonic acid)

IT Neoplasm inhibitors
(lymphoma, radionuclide complexes of tetraazacyclododecanetetramethylephosphonic acid)

IT Neoplasm inhibitors
(myeloma, radionuclide complexes of tetraazacyclododecanetetramethylephosphonic acid)

IT 12064-62-9, Gadolinium oxide
(irradn. of, for Gadolinium-159 prodn.)

IT 68052-85-7, Samarium oxide (152Sm2O3)
(irradn. of, for Samarium-153 prodn.)

IT 1314-36-9, Yttrium trioxide, biological studies
(irradn. of, for Yttrium-90 prodn.)

IT 12055-62-8, biological studies
(irradn. of, for holmium-166 prodn.)

IT 10098-91-6DP, Yttrium-90, complex with tetraazacyclododecanetetramethylenephosphonic acid 13967-65-2DP, Holmium-166, complex with tetraazacyclododecanetetramethylenephosphonic acid 14041-42-0DP, Gadolinium-159, complex with tetraazacyclododecanetetramethylenephosphonic acid 15766-00-4DP, Samarium-153, complex with tetraazacyclododecanetetramethylenephosphonic acid **91987-74-5DP**, complexes with radionuclides
(prepn. of, as bone marrow-suppressing agent, for treatment of cancer and genetic diseases)

IT 294-90-6, 1,4,7,10-Tetraazacyclododecane
(reaction of, with phosphoric acid and formaldehyde)

IT 13598-36-2, Phosphorous acid
(reaction of, with tetraazacyclododecane and formaldehyde)

IT 10294-56-1, Phosphorous acid, reactions
(reaction of, with tetraazacyclododecane formaldehyde)

IT 50-00-0, Formaldehyde, reactions
(reaction of, with tetraazadodecane phosphoric acid)

L28 ANSWER 19 OF 19 USPATFULL
ACCESSION NUMBER: 89:93983 USPATFULL
TITLE: **Bone** marrow suppressing agents
INVENTOR(S): Simon, Jaime, Angleton, TX, United States
Garlich, Joseph R., Lake Jackson, TX, United States
Wilson, David A., Richwood, TX, United States
McMillan, Kenneth, Richwood, TX, United States
PATENT ASSIGNEE(S): The Dow Chemical Company, Midland, MI, United States
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4882142		19891121
APPLICATION INFO.:	US 1988-284875		19881219 (7)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Maples, John S.		
NUMBER OF CLAIMS:	30		
EXEMPLARY CLAIM:	1		
LINE COUNT:	747		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention concerns a method for suppressing **bone** marrow which comprises administering to a mammal at least one **bone** marrow suppressing complex of a radionuclide selected from the group consisting of Samarium-153, Gadolinium-159, and Holmium-166 and 1,4,7,10-tetraazacyclododecanetetramethylenephosphonic acid a physiologically acceptable salt thereof. Suitable compositions for use in this method are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT Bone marrow
(suppression of, with radionuclide complexes of tetraazacyclododecanetetramethylenephosphonic acid, in treatment of cancer and genetic diseases)

IT Neoplasm inhibitors
(Hodgkin's disease, radionuclide complexes of tetraazacyclododecanetetramethylephosphonic acid)

IT Radioelements, compounds
(complexes, with tetraazacyclododecanetetramethylenephosphonic acid, in treatment of cancer and genetic diseases)

IT Neoplasm inhibitors
(leukemia, radionuclide complexes of tetraazacyclododecanetetramethylephosphonic acid)

IT Neoplasm inhibitors
(lymphoma, radionuclide complexes of tetraazacyclododecanetetramethylephosphonic acid)

IT Neoplasm inhibitors
(myeloma, radionuclide complexes of tetraazacyclododecanetetramethylephosphonic acid)

IT 12064-62-9, Gadolinium oxide
(irradn. of, for Gadolinium-159 prodn.)

IT 68052-85-7, Samarium oxide (152Sm2O3)
(irradn. of, for Samarium-153 prodn.)

IT 1314-36-9, Yttrium trioxide, biological studies
(irradn. of, for Yttrium-90 prodn.)

IT 12055-62-8, biological studies
(irradn. of, for holmium-166 prodn.)

IT 10098-91-6DP, Yttrium-90, complex with tetraazacyclododecanetetramethylenephosphonic acid 13967-65-2DP, Holmium-166, complex with tetraazacyclododecanetetramethylenephosphonic acid 14041-42-0DP, Gadolinium-159, complex with tetraazacyclododecanetetramethylenephosphonic acid 15766-00-4DP, Samarium-153, complex with tetraazacyclododecanetetramethylenephosphonic acid **91987-74-5DP**, complexes with radionuclides
(prepn. of, as bone marrow-suppressing agent, for treatment of cancer and genetic diseases)

IT 294-90-6, 1,4,7,10-Tetraazacyclododecane
(reaction of, with phosphoric acid and formaldehyde)

IT 13598-36-2, Phosphorous acid
(reaction of, with tetraazacyclododecane and formaldehyde)

IT 10294-56-1, Phosphorous acid, reactions

(reaction of, with tetraazacyclododecane formaldehyde)

IT 50-00-0, Formaldehyde, reactions
(reaction of, with tetraazadodecane phosphoric acid)

L15 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:300526 CAPLUS
DOCUMENT NUMBER: 134:305337
TITLE: **Aminoalkylenephosphonates** for treatment of bone disorders
INVENTOR(S): Frank, R. Keith
PATENT ASSIGNEE(S): The Dow Chemical Company, USA
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001028567	A2	20010426	WO 2000-US28713	20001017
WO 2001028567	A3	20011129		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1225903	A2	20020731	EP 2000-972234	20001017
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003512331	T2	20030402	JP 2001-531397	20001017

PRIORITY APPLN. INFO.: US 1999-160019P P 19991018
WO 2000-US28713 W 20001017
OTHER SOURCE(S): MARPAT 134:305337

AB A method for preventing or minimizing loss of bone mineral in mammals comprises administering an amt. of an aminoalkylenephosphonate which is effective to prevent or minimize loss of bone mineral d. The **aminoalkylenephosphonates** of the invention should have at least one R-N(Alk-PO3H2)2 group or at least two R2N-Alk-PO3H2 groups (R = aliph. moiety, cyclic moiety; Alk = C1-4 alkylene).

IT Bone, disease
Drug delivery systems
(**aminoalkylenephosphonates** for treatment of bone disorders)

IT Mineral elements, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bone; **aminoalkylenephosphonates** for treatment of bone disorders)

IT Bone
(minerals; **aminoalkylenephosphonates** for treatment of bone disorders)

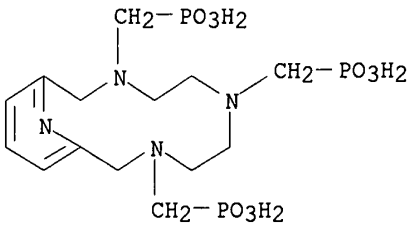
IT 1429-50-1, EDTMP 15827-60-8 66376-36-1, Alendronate 335373-45-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**aminoalkylenephosphonates** for treatment of bone disorders)

IT 13598-36-2D, Phosphonic acid, **aminoalkylenephosphonates**
91987-74-5 150375-17-0 161034-88-4 193003-47-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**aminoalkylenephosphonates** for treatment of bone disorders)

=> FIL REGISTRY

18 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **150375-17-0** REGISTRY
CN Phosphonic acid, [3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triyltris(methylene)]tris- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,6,9,15-Tetraazabicyclo[9.3.1]pentadecane, phosphonic acid deriv.
FS 3D CONCORD
MF C14 H27 N4 O9 P3
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
11 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> SET NOTICE LOGIN DISPLAY

NOTICE SET TO OFF FOR DISPLAY COMMAND
SET COMMAND COMPLETED

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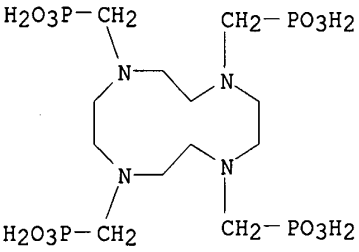
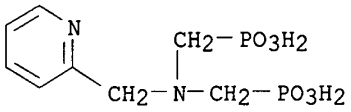
L19 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **91987-74-5** REGISTRY
CN Phosphonic acid, [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayltetrakis(methylene)]tetrakis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10-Tetraazacyclododecane, phosphonic acid deriv.
OTHER NAMES:
CN 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrakis(methylenephosphonic acid)
CN 1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetramethylenephosphonic acid
CN DOTMP
CN DOTP
CN N,N',N'',N'''-Tetrakis(phosphonomethyl)-1,4,7,10-tetraazacyclododecane
FS 3D CONCORD
MF C12 H32 N4 O12 P4
CI COM
LC STN Files: BEILSTEIN*, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CIN, GMELIN*, MEDLINE, PROMT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

52 REFERENCES IN FILE CA (1957 TO DATE)
29 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
52 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L16 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **193003-47-3** REGISTRY
CN Phosphonic acid, [[(2-pyridinylmethyl)imino]bis(methylene)]bis- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C8 H14 N2 O6 P2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



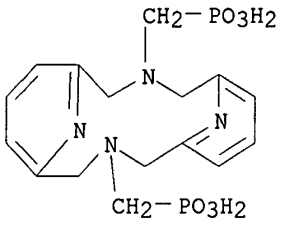
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> SET NOTICE LOGIN DISPLAY

NOTICE SET TO OFF FOR DISPLAY COMMAND
SET COMMAND COMPLETED

17 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **161034-88-4** REGISTRY
CN Phosphonic acid, [3,11,17,18-tetraazatricyclo[11.3.1.15,9]octadeca-1(17),5,7,9(18),13,15-hexaene-3,11-diylbis(methylene)]bis- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C16 H22 N4 O6 P2
SR CA
LC STN Files: CA, CAPLUS, CASREACT, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> SET NOTICE LOGIN DISPLAY

NOTICE SET TO OFF FOR DISPLAY COMMAND
SET COMMAND COMPLETED

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AB The variability of different primary tumors in the susceptibility to metastatic **bone disease** is poorly understood. Factors that determine the viability of metastatic cells are also poorly understood, but may depend in part upon gene expression of PTHrP and the vitamin D receptor. In contrast, much more is known of the manner in which metastatic disease affects bone remodeling to induce osteolytic **bone disease**. Mechanisms include a generalized increase in activation frequency at sites close to metastatic tissue, an imbalance between the amount of bone formed and that resorbed within resorption cavities, and uncoupling of bone formation from bone resorption. The greatest morbidity from metastatic **bone disease** arises from osteolytic disease and gives rise to hypercalcemia, bone pain, and fractures. Because osteolysis is primarily mediated by the activation of osteoclasts, there has been a great deal of interest in the use of agents which primarily affect bone metabolism to alter the natural history of metastatic **bone disease**. Nonsteroidal antiinflammatory agents and cytotoxic agents are capable of inducing responses in bone, but are limited by their toxicity when effective doses are utilized. The use of calcitonin in the long-term suppression of osteolysis has also been disappointing. The **bisphosphonates** are, however, capable of inducing sustained decreases in osteoclast activity and numbers in patients with osteolytic **bone disease**. There are now several studies which have examined the effects of the **bisphosphonates** on skeletal morbidity in breast cancer. Both clodronate and pamidronate decrease the incidence of hypercalcemia, bone pain, and pathological fractures, but do not significantly alter mortality.(ABSTRACT TRUNCATED AT 250 WORDS)

L33 ANSWER 16 OF 155 MEDLINE
ACCESSION NUMBER: 2001073697 MEDLINE
DOCUMENT NUMBER: 20562996 PubMed ID: 11110597
TITLE: Management of bone metastases.
AUTHOR: Coleman R E
CORPORATE SOURCE: Yorkshire Cancer Research Department of Clinical Oncology, Cancer Research Center, Weston Park Hospital, Sheffield, England.. r.e.coleman@sheffield.ac.uk
SOURCE: ONCOLOGIST, (2000) 5 (6) 463-70. Ref: 36
Journal code: 9607837. ISSN: 1083-7159.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010103

AB Metastatic **bone disease** develops as a result of the many interactions between tumor cells and bone cells. This leads to disruption of normal bone metabolism, with the increased osteoclast activity seen in most, if not all, tumor types providing a rational target for treatment. The clinical course of metastatic **bone disease** in multiple myeloma, breast and prostate cancers is relatively long, with patients experiencing sequential skeletal complications over a period of several years. These include bone pain, fractures, hypercalcemia, and spinal cord compression, all of which may profoundly impair a patient's quality of life. External beam radiotherapy and systemic endocrine and cytotoxic treatments are the mainstay of treatment in advanced cancers. However, it is now clear that the **bisphosphonates** provide an additional treatment strategy, which reduces both the symptoms and complications of bone involvement.

Additionally, new specific molecules such as osteoprotogerin have been developed that are based on our improved understanding of the cellular signaling mechanisms involved in cancer-induced **bone disease**. These potent molecules are now entering clinical trials. Ongoing research is aimed at trying to define the optimum route, dose, schedule and type of **bisphosphonate** in metastatic **bone disease** and its use in the **prevention** and treatment of osteoporosis in cancer patients. In vitro suggestions of direct anticancer activity and some promising clinical data in early breast cancer have resulted in considerable interest in the possible adjuvant use of **bisphosphonates** to inhibit the development of bone metastases.

L33 ANSWER 17 OF 155 MEDLINE
ACCESSION NUMBER: 1999281706 MEDLINE
DOCUMENT NUMBER: 99281706 PubMed ID: 10355575
TITLE: Double-blind, randomised, placebo-controlled, dose-finding study of oral ibandronate in patients with metastatic **bone disease**.
AUTHOR: Coleman R E; Purohit O P; Black C; Vinholes J J; Schlosser K; Huss H; Quinn K J; Kanis J
CORPORATE SOURCE: Yorkshire Cancer Research Department of Clinical Oncology, Weston Park Hospital, Sheffield, UK.
SOURCE: ANNALS OF ONCOLOGY, (1999 Mar) 10 (3) 311-6.
Journal code: 9007735. ISSN: 0923-7534.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990727
Last Updated on STN: 19990727
Entered Medline: 19990712

AB BACKGROUND: **Bisphosphonates** are an important component of the treatment of metastatic **bone disease** but more potent, oral formulations are required to improve the effectiveness and convenience of treatment. An oral formulation of the new **bisphosphonate**, ibandronate (BM 21.0955) has recently been developed. PATIENTS AND METHODS: One hundred ten patients with bone metastases (77 breast, 16, prostate, 3 myeloma, 14 others) were recruited from a single institution to this double blind placebo-controlled evaluation of four oral dose levels (5, 10, 20 and 50 mg) of ibandronate. No changes in systemic anti-cancer treatment were allowed in the month before commencing treatment or during the study period. After an initial four-week tolerability phase, patients could continue on treatment for a further three months without unblinding; patients initially allocated to placebo received ibandronate 50 mg. The primary endpoint was urinary calcium excretion (UCCR). Bone resorption was also assessed by measurement of pyridinoline (Pyr), deoxypyridinoline (Dpd), and the N-terminal (NTX) and C-terminal (Crosslaps) portions of the collagen crosslinking molecules. RESULTS: Two patients did not receive any trial medication thus, 108 patients were evaluable for safety. Ninety-two patients were evaluable for efficacy. A dose dependent reduction was observed in both UCCR and collagen crosslink excretion. At the 50 mg dose level, the percentage reductions from baseline in UCCR, Pyr, Dpd, Crosslaps and NTX were 71%, 28%, 39%, 80% and 74% respectively. One or more gastrointestinal (GI) adverse events occurring in the first month of treatment were reported by six (30%), seven (33%), nine (39%), nine (41%) and eleven (50%) patients at the placebo, 5, 10, 20 and 50 mg dose levels respectively. One patient (20 mg dose) developed radiographically

confirmed oesophageal ulceration. GI tolerability may have been adversely affected by concomitant administration of non-steroidal anti-inflammatory agents. Nine (8%) patients stopped treatment within the first month due to GI intolerability but these patients were evenly distributed across the five treatment groups. There was no difference in non-GI adverse events between groups. CONCLUSIONS: Oral ibandronate has potent effects on the rate of bone resorption at doses which are generally well tolerated. Further development is appropriate to evaluate the effects of long-term administration in the **prevention** of metastatic **bone disease** and the management of established skeletal metastases.

L33 ANSWER 18 OF 155 MEDLINE
ACCESSION NUMBER: 92183613 MEDLINE
DOCUMENT NUMBER: 92183613 PubMed ID: 1724640
TITLE: **Bisphosphonates**. Pharmacology and use in the treatment of tumour-induced hypercalcaemic and metastatic **bone disease**.
AUTHOR: Fleisch H
CORPORATE SOURCE: Department of Pathophysiology, University of Berne, Switzerland.
SOURCE: DRUGS, (1991 Dec) 42 (6) 919-44. Ref: 219
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
(REVIEW, MULTICASE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920424
Last Updated on STN: 19960129
Entered Medline: 19920416

AB The geminal **bisphosphonates** are a new class of drugs characterised by a P-C-P bond. Consequently, they are analogues of pyrophosphate, but are resistant to chemical and enzymatic hydrolysis. The **bisphosphonates** bind strongly to hydroxyapatite crystals and inhibit their formation and dissolution. This physicochemical effect leads in vivo to the **prevention** of soft tissue calcification and, in some instances, inhibition of normal calcification. The main effect is to inhibit bone resorption, but in contrast to the effect on mineralisation, the mechanism involved is cellular. These various effects vary greatly according to the structure of the individual **bisphosphonate**. The half-life of circulating **bisphosphonates** is very brief, in the order of minutes to hours. 20% to 50% of a given dose is taken up by the skeleton, the rest being excreted in the urine. The half-life in bone is far longer and depends upon the turnover rate of the skeleton itself. **Bisphosphonates** are very well tolerated; the relatively few adverse events that have been associated with their use are specific for each compound. **Bisphosphonates** have been used to treat various clinical conditions, namely ectopic calcification, ectopic bone formation, Paget's disease, osteoporosis and increased osteolysis of malignant origin. The three compounds commercially available for use in tumour-induced **bone disease** are in order of increasing potency, etidronate, clodronate and pamidronate. Most data have been obtained with the latter two agents. By inhibiting bone resorption, they correct hypercalcaemia and hypercalciuria, reduce pain, the occurrence of fractures, as well as the development of new osteolytic lesions, and in consequence improve the quality of life. In view of these actions, of their excellent tolerability and of the fact that they are active for relatively long periods, these compounds are, after rehydration, the drugs

of choice in tumour-induced **bone disease** and an excellent auxiliary to the drugs used in oncology.

present in newer generations of **bisphosphonates**.
RECOMMENDATIONS: **Bisphosphonate** therapies may be considered as an alternative to ovarian hormone therapy in postmenopausal osteopenic or osteoporotic women who cannot or will not tolerate ovarian hormone therapy. They should also be considered in treating male osteoporosis and steroid-induced bone loss. Combination therapy with estrogen may be effective, although more research is needed. Combination therapy with calcium supplements is recommended. **Bisphosphonate** therapies should be restricted to postmenopausal patients with osteopenia or established osteoporosis and are not yet recommended for younger perimenopausal women as prophylaxis.

L33 ANSWER 12 OF 155 MEDLINE
ACCESSION NUMBER: 97287841 MEDLINE
DOCUMENT NUMBER: 97287841 PubMed ID: 9142969
TITLE: Rationale for the use of **bisphosphonates** in breast cancer.
AUTHOR: Kanis J A
CORPORATE SOURCE: Department of Human Metabolism & Clinical Biochemistry, University of Sheffield Medical School, UK.
SOURCE: ACTA ONCOLOGICA, (1996) 35 Suppl 5 61-7. Ref: 32
Journal code: 8709065. ISSN: 0284-186X.
PUB. COUNTRY: Norway
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970602
Last Updated on STN: 19970602
Entered Medline: 19970522

AB The variability of different breast cancers in the susceptibility to metastatic **bone disease** is poorly understood. Factors that determine the viability of metastatic cells are also poorly understood, but may depend in part upon gene expression of PTHrP and the vitamin D receptor. In contrast, much more is known of the manner in which metastatic breast disease affects bone remodelling to induce osteolytic **bone disease**. Mechanisms include a generalized increase in activation frequency at sites close to metastatic tissue, an imbalance between the amount of bone formed and that resorbed within resorption cavities, and uncoupling of bone formation from bone resorption. The greatest morbidity from metastatic **bone disease** arises from osteolytic disease and gives rise to hypercalcaemia, bone pain and fractures. Since osteolysis is primarily mediated by the activation of osteoclasts, there has been a great deal of interest in the use of agents which primarily affect bone metabolism to alter the natural history of metastatic **bone disease**. Non-steroidal anti-inflammatory agents and cytotoxic agents are capable of inducing responses in bone, but are limited by their toxicity when effective doses are utilized. The use of calcitonin in the long-term suppression of osteolysis has also been disappointing. The **bisphosphonates** are, however, capable of inducing sustained decreases in osteoclast activity and numbers in patients with osteolytic **bone disease**. There are now several studies which have examined the effects of the **bisphosphonates** on skeletal morbidity in breast cancer. Both clodronate and pamidronate decrease the incidence of hypercalcaemia, bone pain and pathological fractures, but do not significantly alter mortality. Given, however, the unchanging survival in patients with metastatic **bone disease**, significant improvements in the quality of remaining life is an important therapeutic effect.

L33 ANSWER 13 OF 155 MEDLINE
ACCESSION NUMBER: 94061789 MEDLINE
DOCUMENT NUMBER: 94061789 PubMed ID: 8242577
TITLE: New **bisphosphonates** in the treatment of bone metastases.
AUTHOR: Averbuch S D
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ 07065-0914.
SOURCE: CANCER, (1993 Dec 1) 72 (11 Suppl) 3443-52. Ref: 93
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940201
Last Updated on STN: 19940201
Entered Medline: 19931227

AB Normal skeletal integrity is maintained by physiological bone turnover through a coupled process of bone resorption, mediated by osteoclasts, followed by new bone formation, mediated by osteoblasts. Major features of the pathogenesis of cancer-associated skeletal destruction are enhanced osteoclast-mediated bone resorption and disruption of normal bone formation. In this article, the literature on the pathogenesis and clinical manifestations of metastatic **bone disease** is discussed. Animal and clinical trials investigating novel bone targeted agents, emphasizing the **bisphosphonates**, are critically assessed. The most frequent clinical manifestations of bone metastases are pain, fracture, immobility, spinal cord compression, and hypercalcemia. New treatments under study for patients with bone metastases include agents specifically targeted to the skeleton such as bone-seeking radioisotopes and **bisphosphonates**. Studies in animal models of metastatic **bone disease** show that these **bisphosphonates** are able to inhibit tumor-induced osteolysis and are potentially useful in this condition. **Bisphosphonates** have been investigated in several clinical trials of patients with skeletal metastases from breast cancer, prostate cancer, and multiple myeloma. Overall, the studies investigating bone targeted radioisotopes or **bisphosphonates** for the treatment of morbidity due to skeletal metastases have been inconclusive. An improved understanding of the pathogenesis of metastatic **bone disease** and preclinical studies with **bisphosphonates** suggest that these agents may have a role in the treatment of this disorder. Additional trials of new generation **bisphosphonates**, employing a rigorously controlled, randomized study design with adequate numbers of subjects, are needed to demonstrate the safety and efficacy of this class of agents in this setting.

L33 ANSWER 14 OF 155 MEDLINE
ACCESSION NUMBER: 2001033504 MEDLINE
DOCUMENT NUMBER: 20365557 PubMed ID: 10910187
TITLE: Treatment of **bone diseases** with **bisphosphonates**, excluding osteoporosis.
AUTHOR: Devogelaer J P
CORPORATE SOURCE: Department of Rheumatology, St-Luc University Hospital, Universite Catholique de Louvain, Brussels, Belgium.. Devogelaer@ruma.ucl.ac.be
SOURCE: CURRENT OPINION IN RHEUMATOLOGY, (2000 Jul) 12 (4) 331-5. Ref: 30
Journal code: 9000851. ISSN: 1040-8711.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001130

AB The main biologic action of **bisphosphonates** consists of the inhibition of osteoclastic bone resorption, and, at least, for the drugs introduced after etidronate, without any significant inhibition of bone mineralization. **Bisphosphonates** therefore play a major role in conditions that are characterized, at least partly, by an increased bone resorption. Primary and secondary osteoporosis by far constitute the most widespread indications for **bisphosphonates**, mostly because recent published trials have demonstrated their ability to prevent fractures. Potentially crippling conditions such as symptomatic Paget disease of bone remain a major therapeutic challenge for **bisphosphonates**, but the **prevention** of the major complications such as sarcoma has still to be proven. The availability of more potent **bisphosphonates**, less toxic for bones, has certainly widened the therapeutic interventions to asymptomatic patients, bearing in mind the various potential troublesome complications. Fibrous dysplasia resembles, in certain aspects, Paget disease; it is therefore not surprising that **bisphosphonate** therapy has been proposed in this indication. With the aging of world populations, more and more cancers will be diagnosed. For those with a bone metastatic propensity or malignant hematologic condition, such as multiple myeloma, the most recent generation of more potent **bisphosphonates** may bring more comfort to crippled patients and even, hopefully, have a direct antitumoral activity, if used synergistically with the armamentarium already available to the clinician. New indications for **bisphosphonates** include osteogenesis imperfecta both in children and adults. In the future, they might be used in the **prevention** of erosions in rheumatoid arthritis and of loosening of joint prostheses, as well as possibly in osteoarthritis. Now that the fear of theoretically freezing bone remodeling has been reasonably dismissed, potential uses for **bisphosphonates** might be considered nearly infinite.

L33 ANSWER 15 OF 155 MEDLINE
ACCESSION NUMBER: 96019099 MEDLINE
DOCUMENT NUMBER: 96019099 PubMed ID: 8579890
TITLE: Bone and cancer: pathophysiology and treatment of metastases.
AUTHOR: Kanis J A
CORPORATE SOURCE: WHO Collaborating Centre for Metabolic Bone Disease, Department of Human Metabolism & Clinical Biochemistry, University of Sheffield Medical School, UK.
SOURCE: BONE, (1995 Aug) 17 (2 Suppl) 101S-105S. Ref: 29
Journal code: 8504048. ISSN: 8756-3282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960327
Last Updated on STN: 19960327
Entered Medline: 19960320

L33 ANSWER 30 OF 155 MEDLINE
ACCESSION NUMBER: 97226054 MEDLINE
DOCUMENT NUMBER: 97226054 PubMed ID: 9073324
TITLE: **Bisphosphonates**: preclinical aspects and use in osteoporosis.
AUTHOR: Fleisch H A
CORPORATE SOURCE: Department of Pathophysiology, University of Bern, Switzerland.
SOURCE: ANNALS OF MEDICINE, (1997 Feb) 29 (1) 55-62. Ref: 49
Journal code: 8906388. ISSN: 0785-3890.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970620
Last Updated on STN: 19970620
Entered Medline: 19970612

AB The **bisphosphonates** are synthetic compounds characterized by a P-C-P bond. They have a strong affinity to calcium phosphates and hence to bone mineral. In vitro they inhibit both formation and dissolution of the latter. Many of the **bisphosphonates** inhibit bone resorption, the newest compounds being 10,000 times more active than etidronate, the first **bisphosphonate** described. The antiresorbing effect is cell mediated, partly by a direct action on the osteoclasts, partly through the osteoblasts, which produce an inhibitor of osteoclastic recruitment. When given in large amounts, some **bisphosphonates** can also inhibit normal and ectopic mineralization through a physical-chemical inhibition of crystal growth. In the growing rat the inhibition of resorption is accompanied by an increase in intestinal absorption and an increased balance of calcium. **Bisphosphonates** also prevent various types of experimental osteoporosis, such as after immobilization, ovariectomy, orchidectomy, administration of corticosteroids, or low calcium diet. The P-C-P bond of the **bisphosphonates** is completely resistant to enzymatic hydrolysis. The **bisphosphonates** studied up to now, such as etidronate, clodronate, pamidronate, and alendronate, are absorbed, stored, and excreted unaltered. The intestinal absorption of the **bisphosphonates** is low, between 1% or less and 10% of the amount ingested. The newer **bisphosphonates** are at the lower end of the scale. The absorption diminishes when the compounds are given with food, especially in the presence of calcium. **Bisphosphonates** are rapidly cleared from plasma, 20%-80% being deposited in bone and the remainder excreted in the urine. In bone, they deposit at sites of mineralization as well as under the osteoclasts. In contrast to plasma, the half-life in bone is very long, partially as long as the half-life of the bone in which they are deposited. In humans, **bisphosphonates** are used successfully in diseases with increased bone turnover, such as Paget's disease, tumoural **bone disease**, as well as in osteoporosis. Various **bisphosphonates**, such as alendronate, clodronate, etidronate, ibandronate, pamidronate, and tiludronate, have been investigated in osteoporosis. All inhibit bone loss in postmenopausal women and increase bone mass. Furthermore, **bisphosphonates** are also effective in **preventing** bone loss both in corticosteroid-treated and in immobilized patients. The effect on the rate of fractures has recently been proven for alendronate. In humans, the adverse effects depend upon the compound and the amount given. For etidronate, practically the only adverse effect is an inhibition of mineralization. The aminoderivatives induce for a period of

2-3 days a syndrome with pyrexia, which shows a similitude with an acute phase reaction. The more potent compounds can induce gastrointestinal disturbances, sometimes oesophagitis, when given orally.
Bisphosphonates are an important addition to the therapeutic possibilities in the **prevention** and treatment of osteoporosis.

ACCESSION NUMBER: 1999349894 MEDLINE
DOCUMENT NUMBER: 99349894 PubMed ID: 10423031
TITLE: **Bisphosphonates**: from the laboratory to the clinic and back again.
AUTHOR: Russell R G; Rogers M J
CORPORATE SOURCE: Division of Biochemical and Musculoskeletal Metabolism, Human Metabolism and Clinical Biochemistry, University of Sheffield Medical School, UK.
SOURCE: BONE, (1999 Jul) 25 (1) 97-106. Ref: 106
Journal code: 8504048. ISSN: 8756-3282.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990923

AB **Bisphosphonates** (BPs) used as inhibitors of bone resorption all contain two phosphonate groups attached to a single carbon atom, forming a "P-C-P" structure. The **bisphosphonates** are therefore stable analogues of naturally occuring pyrophosphate-containing compounds, which now helps to explain their intracellular as well as their extracellular modes of action. **Bisphosphonates** adsorb to bone mineral and inhibit bone resorption. The mode of action of **bisphosphonates** was originally ascribed to physico-chemical effects on hydroxyapatite crystals, but it has gradually become clear that cellular effects must also be involved. The marked structure-activity relationships observed among more complex compounds indicate that the pharmacophore required for maximal activity not only depends upon the **bisphosphonate** moiety but also on key features, e.g., nitrogen substitution in alkyl or heterocyclic side chains. Several **bisphosphonates** (e.g., etidronate, clodronate, pamidronate, alendronate, tiludronate, risedronate, and ibandronate) are established as effective treatments in clinical disorders such as Paget's disease of bone, myeloma, and bone metastases. **Bisphosphonates** are also now well established as successful antiresorptive agents for the **prevention** and treatment of osteoporosis. In particular, etidronate and alendronate are approved as therapies in many countries, and both can increase bone mass and produce a reduction in fracture rates to approximately half of control rates at the spine, hip, and other sites in postmenopausal women. In addition to inhibition of osteoclasts, the ability of **bisphosphonates** to reduce the activation frequency and birth rates of new bone remodeling units, and possibly to enhance osteon mineralisation, may also contribute to the reduction in fractures. The clinical pharmacology of **bisphosphonates** is characterized by low intestinal absorption, but highly selective localization and retention in bone. Significant side effects are minimal. Current issues with **bisphosphonates** include the introduction of new compounds, the choice of therapeutic regimen (e.g., the use of intermittent dosing rather than continuous), intravenous vs. oral therapy, the optimal duration of therapy, the combination with other drugs, and extension of their use to other conditions, including steroid-associated osteoporosis, male osteoporosis, arthritis, and osteopenic disorders in childhood. **Bisphosphonates** inhibit bone resorption by being selectively taken up and adsorbed to mineral surfaces in bone, where they interfere with the action of osteoclasts. It is likely that **bisphosphonates** are internalized by osteoclasts and interfere with specific biochemical processes and induce apoptosis. The molecular mechanisms by which these

effects are brought about are becoming clearer. Recent studies show that **bisphosphonates** can be classified into at least two groups with different modes of action. **Bisphosphonates** that closely resemble pyrophosphate (such as clodronate and etidronate) can be metabolically incorporated into nonhydrolysable analogues of ATP that may inhibit ATP-dependent intracellular enzymes. The more potent, nitrogen-containing **bisphosphonates** (such as pamidronate, alendronate, risedronate, and ibandronate) are not metabolized in this way but can inhibit enzymes of the mevalonate pathway, thereby **preventing** the biosynthesis of isoprenoid compounds that are essential for the posttranslational modification of small GTPases. The inhibition of protein prenylation and the disruption of the function of these key regulatory proteins explains the loss of osteoclast activity and induction of apoptosis. These different modes of action might account for subtle differences between compounds in terms of their clinical effects. In conclusion, **bisphosphonates** are now established as an important class of drugs for the treatment of **bone diseases**, and their mode of action is being unravelled. As a result, their full therapeutic potential is gradual

L33 ANSWER 28 OF 155 MEDLINE

L33 ANSWER 25 OF 155 MEDLINE
ACCESSION NUMBER: 2000047600 MEDLINE
DOCUMENT NUMBER: 20047600 PubMed ID: 10582775
TITLE: New **bisphosphonates** in the treatment of **bone diseases**.
AUTHOR: Gatti D; Adami S
CORPORATE SOURCE: University Hospital of Valeggio, University of Verona, Italy.
SOURCE: DRUGS AND AGING, (1999 Oct) 15 (4) 285-96. Ref: 93
Journal code: 9102074. ISSN: 1170-229X.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991214

AB **Bisphosphonates** are pyrophosphate analogues, in which the oxygen in P-O-P has been replaced by a carbon, resulting in a P-C-P structure. They are characterised by a strong anti-osteoclastic activity and for this pharmacological property they are now considered the treatment of choice for Paget's disease of the bone, malignant hypercalcaemia and bone metastases. Etidronate, clodronate and pamidronate have been registered in several countries for these indications. Etidronate and alendronate are also extensively used for the **prevention** and treatment of postmenopausal and senile osteoporosis. In this article, we review the most recent findings on the newest **bisphosphonates**, which will become available in the near future. The aminobisphosphonate risedronate is undergoing a huge programme of clinical development for the treatment of osteoporosis. In a study of the **prevention** of early postmenopausal bone loss, oral risedronate 5 mg fully prevented the bone loss observed in the placebo group. Similar effects have been observed with an intermittent dosage regimen of oral risedronate 30 mg/day for 2 out of 12 weeks, which corresponds to 5 mg/day in terms of cumulative dose. With lower doses [5 mg on alternate fortnights (2 weeks)] the **prevention** of bone loss was half that observed with continuous 5 mg/day therapy, indicating that this might not yet be the maximum effective dose. The use of intermittent intravenous **bisphosphonates** for osteoporosis therapy has been pioneered by studies with clodronate, pamidronate and alendronate. This treatment regimen has been chosen for an extensive clinical development programme for ibandronate. In a phase 2 study, this new **bisphosphonate** was administered as an intravenous bolus (0.25, 0.5, 1 or 2 mg) every 3 months for a year, with increases in spinal bone mass of 5.2%. Tiludronate, alendronate and risedronate have been recently introduced for the treatment of Paget's disease of bone. Daily doses of tiludronate 400 mg, alendronate 40 mg and risedronate 30 mg for 3 to 6 months have been shown to be superior to etidronate 400 mg/day. The intravenous administration of ibandronate, zoledronate and alendronate (40 mg, 10 mg and 5 mg, respectively) have achieved the normalisation of serum alkaline phosphatase in more than 70% of the patients and these treatments may provide an alternative for patients intolerant oral **bisphosphonates**. Intravenous ibandronate has been also developed for the treatment of hypercalcaemia of malignancy. The effective doses ranged from 2 to 4 mg. Zoledronate appears to be the most powerful **bisphosphonate** under investigation, and the effective doses used in cancer hypercalcaemia are as low as 1 to 2 mg. The new generation of **bisphosphonates** are likely to increase clinical options in terms

of administration regimens, but their real advantage over those already available in terms of clinical efficacy remains uncertain.

L33 ANSWER 26 OF 155 MEDLINE

L33 ANSWER 20 OF 155 MEDLINE
ACCESSION NUMBER: 2000470008 MEDLINE
DOCUMENT NUMBER: 20390260 PubMed ID: 10934603
TITLE: [**Bisphosphonates** in pharmacotherapy of **bone diseases**].
Bisfosfonaty v farmakoterapii kostnykh zabolevanii.
AUTHOR: Iur'ieva E A; Matkovskaia T A; Elagina I A; Stoliarov Iu Iu
CORPORATE SOURCE: Research Institute of Pediatry and Infant Surgery, Moscow, Russia.
SOURCE: EKSPERIMENTALNAIA I KLINICHESKAIA FARMAKOLOGIIA, (2000 May-Jun) 63 (3) 74-9. Ref: 53
Journal code: 9215981. ISSN: 0869-2092.
PUB. COUNTRY: RUSSIA: Russian Federation
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20000929

AB **Bisphosphonates** represent a new class of drugs that has been developed in the past three decades for the treatment of various **bone diseases** and calcium metabolism disorders. Possessing high affinity to the bone-forming minerals, these substances can be used as inhibitors of the ectopic calcification and bone resorption. **Bisphosphonates** not only prevent from the loss of bones in the case of osteoporosis of various types (e.g., after the menopause), but provide for an increase in the bone mineral density as well. Therefore, these drugs offer an important additional means of therapy in cases of osteoporosis and other bone disorders.

L33 ANSWER 19 OF 155 MEDLINE
ACCESSION NUMBER: 2003039321 MEDLINE
DOCUMENT NUMBER: 22434869 PubMed ID: 12548587
TITLE: Effectiveness and cost of **bisphosphonate** therapy in tumor **bone disease**.
AUTHOR: Body Jean-Jacques
CORPORATE SOURCE: Supportive Care Clinic and Clinic of Endocrinology/Bone Diseases, Department of Medicine, Institut J. Bordet, Universite Libre de Bruxelles, Brussels, Belgium.. jj.body@bordet.be
SOURCE: CANCER, (2003 Feb 1) 97 (3 Suppl) 859-65. Ref: 30
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030128
Last Updated on STN: 20030416
Entered Medline: 20030414

AB BACKGROUND: Tumor-induced osteolysis due to breast carcinoma and myeloma is responsible for a considerable morbidity that severely impairs patients'quality of life. Osteoclast-mediated bone resorption is reported to be increased markedly in patients with tumor **bone disease** and can be inhibited by **bisphosphonate** therapy. METHODS: The incidence of skeletal complications and the effectiveness of **bisphosphonate** therapy in patients with breast carcinoma metastatic to bone or in those with myeloma were derived from large-scale, long-term, placebo-controlled trials with clodronate or pamidronate. To the authors' knowledge, there are few studies published to date evaluating the cost-effectiveness of **bisphosphonate** therapy, and the majority that do exist often are based on models and are applicable only to a particular health care system. RESULTS: From the placebo groups of the above-mentioned trials, one can estimate that approximately 25-40% of the patients with breast carcinoma metastatic to bone will require radiotherapy for bone pain and approximately 17-50% will sustain incident vertebral fractures yearly. The incidence of complications is reported to be lower in myeloma patients. The prolonged administration of **bisphosphonates** reportedly can reduce the frequency of skeletal-related events by approximately 25-50%. Maximal efficacy appears to have been achieved with the current therapeutic schemes based on monthly intravenous infusions. Beneficial effects appear to be obtained more readily using the intravenous route rather than the oral route. The costs of **bisphosphonate** therapy appear to be higher than the cost savings from the **prevention** of skeletal-related events. The costs per quality of life-adjusted year have been estimated to be > $100,000, but more research is needed. Limited data suggest that zoledronic acid will not reduce treatment costs but the short infusion time will lead to substantial time savings for patients and for outpatient oncology facilities. CONCLUSIONS: As is the case for many agents used in oncology, **bisphosphonates** remain a relatively expensive therapy. More studies are needed to evaluate their cost-effectiveness ratio correctly. A ceiling effect has been reached with current therapeutic schemes and tailoring therapy to the individual patient needs to be evaluated correctly to increase therapeutic effectiveness and improve quality of life further without increasing treatment costs.
DOI 10.1002/cncr.11139

L33 ANSWER 1 OF 155 MEDLINE
ACCESSION NUMBER: 90200760 MEDLINE
DOCUMENT NUMBER: 90200760 PubMed ID: 2630251
TITLE: Antiresorptive dose-response relationships across three generations of **bisphosphonates**.
AUTHOR: Sietsema W K; Ebetino F H; Salvagno A M; Bevan J A
CORPORATE SOURCE: Norwich Eaton Pharmaceuticals (A Procter and Gamble Co.), Woods Corners Laboratories, NY 13815.
SOURCE: DRUGS UNDER EXPERIMENTAL AND CLINICAL RESEARCH, (1989) 15 (9) 389-96.
Journal code: 7802135. ISSN: 0378-6501.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199005
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19900601
Entered Medline: 19900508

AB The first generation of **bisphosphonates** was discovered in the late 1960s and is characterized by short alkyl or halide side-chains. Well known representatives of this class are 1-hydroxyethane-1,1-**bisphosphonate** (etidronate) and dichloromethane **bisphosphonate** (clodronate). The antiresorptive activity of these and other analogues was measured in an assay in which a drug was administered for 7 days to growing rats, followed by a morphological assessment of bone volume. In this model, the first generation analogues have antiresorptive activity at dose levels from 0.1 to 10 mg P/kg. Some first generation analogues are now used to treat metabolic **bone disease** but, when given orally, their efficacy in aggressive resorptive disease may be limited because of low potency. A second generation of **bisphosphonates**, characterized by an amino terminal group and a higher antiresorptive potency, includes 3-amino-1-hydroxypropane-1,1-**bisphosphonate** (pamidronate) and 4-amino-1-hydroxybutane-1,1-**bisphosphonate**. Their antiresorptive activity in growing rats ranges from 0.01 to 1 mg P/kg. In the 1980s a third generation of **bisphosphonates**, characterized by a cyclic chain, was synthesized. It includes series of pyridinyl ethane **bisphosphonates**, pyridinyl aminomethane **bisphosphonates**, indan **bisphosphonates**, cyclopentane **bisphosphonates**, piperidyl ethane **bisphosphonates**, pyridinyl and piperidyl hydroxyethane **bisphosphonates**, piperidinylidene aminomethane **bisphosphonates**, and pyridinyl oxa- and thiomethane **bisphosphonates**. Several of these show antiresorptive activity in growing rats as low as 0.001 mg P/kg. Many of the first-, second- and third-generation **bisphosphonates** have been tested in a model of retinoid-induced bone resorption, and in this model the rank ordering of potency is similar, though somewhat larger doses of **bisphosphonate** are required to block the resorption induced by the retinoid.(ABSTRACT TRUNCATED AT 250 WORDS)

L33 ANSWER 2 OF 155 MEDLINE
ACCESSION NUMBER: 2003107059 IN-PROCESS
DOCUMENT NUMBER: 22506909 PubMed ID: 12619933
TITLE: Zoledronic acid treatment of 5T2MM-bearing mice inhibits the development of myeloma **bone disease** : evidence for decreased osteolysis, tumor burden and angiogenesis, and increased survival.
AUTHOR: Croucher Peter I; De Hendrik Raeve; Perry Mark J; Hijzen Anja; Shipman Claire M; Lippitt Jennifer; Green Jonathan;

Van Marck Eric; Van Camp Ben; Vanderkerken Karin
CORPORATE SOURCE: Nuffield Department of Orthopaedic Surgery, University of Oxford, Nuffield Orthopaedic Centre, Headington, Oxford, United Kingdom.. peter.croucher@ndos.ox.ac.uk
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (2003 Mar) 18 (3) 482-92.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030307
Last Updated on STN: 20030307

AB Multiple myeloma is characterized by the growth of plasma cells in the bone marrow and the development of osteolytic **bone disease**. Myeloma cells are found closely associated with bone, and targeting this environment may therefore affect both the **bone disease** and the growth of myeloma cells. We have investigated the effect of the potent **bisphosphonate**, zoledronic acid, on the development of **bone disease**, tumor burden, and disease-free survival in the 5T2MM model of myeloma. 5T2MM murine myeloma cells were injected intravenously into C57BL/KaLwRij mice. After 8 weeks, all animals had a paraprotein. Animals were treated with zoledronic acid (120 microg/kg, subcutaneously, twice weekly) or vehicle, from the time of tumor cell injection or from paraprotein detection for 12 or 4 weeks, respectively. All animals injected with tumor cells developed osteolytic lesions, a decrease in cancellous bone volume, an increase in osteoclast perimeter, and a decrease in bone mineral density. Zoledronic acid prevented the formation of lesions, prevented cancellous bone loss and **loss** of **bone mineral** density, and reduced osteoclast perimeter. Zoledronic acid also decreased paraprotein concentration, decreased tumor burden, and reduced angiogenesis. In separate experiments, Kaplan-Meier analysis demonstrated a significant increase in survival after treatment with zoledronic acid when compared with control (47 vs. 35 days). A single dose of zoledronic acid was also shown to be effective in **preventing** the development of osteolytic **bone disease**. These data show that zoledronic acid is able to prevent the development of osteolytic **bone disease**, decrease tumor burden in bone, and increase survival in a model of established myeloma.

L33 ANSWER 3 OF 155 MEDLINE
ACCESSION NUMBER: 2002444527 MEDLINE
DOCUMENT NUMBER: 22191564 PubMed ID: 12202673
TITLE: American Society of Clinical Oncology clinical practice guidelines: the role of **bisphosphonates** in multiple myeloma.
AUTHOR: Berenson James R; Hillner Bruce E; Kyle Robert A; Anderson Ken; Lipton Allan; Yee Gary C; Biermann J Sybil
CORPORATE SOURCE: American Society of Clinical Oncology, Health Services Research Department, Alexandria, VA 22314, USA. (American Society of Clinical Oncology Bisphosphonates Expert Panel).
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, (2002 Sep 1) 20 (17) 3719-36.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (GUIDELINE)
Journal; Article; (JOURNAL ARTICLE)
(PRACTICE GUIDELINE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020831

Last Updated on STN: 20020919
Entered Medline: 20020918

AB PURPOSE: To determine clinical practice guidelines for the use of **bisphosphonates** in the **prevention** and treatment of lytic **bone disease** in multiple myeloma and to determine their respective role relative to other conventional therapies for this condition. METHODS: An expert multidisciplinary Panel reviewed pertinent information from the published literature through January 2002. Values for levels of evidence and grade of recommendation were assigned by expert reviewers and approved by the Panel. Expert consensus was used if there were insufficient published data. The Panel addressed which patients to treat and when to treat them in the course of their disease. Additionally, specific drug delivery issues, duration of therapy, initiation of treatment and management of treatment of lytic **bone disease** was reviewed and compared with other forms of therapy for lytic bone lesions. Finally, the Panel discussed patient and physician expectations associated with this therapy for bony metastases, as well as public policy implications related to the use of **bisphosphonates** . The guidelines underwent external review by selected physicians, by the Health Services Research Committee members, and by the ASCO Board of Directors. RESULTS: The available evidence involving randomized controlled trials is modest but supports that oral clodronate, intravenous pamidronate, and intravenous zoledronic acid are superior to placebo in reducing skeletal complications. A reduction in vertebral fractures has consistently been seen across all studies. No agent has shown a definitive survival benefit. Intravenous zoledronic acid has recently been shown to be as effective as intravenous pamidronate. Because there are no direct comparisons between clodronate and pamidronate or zoledronic acid, the superiority of one agent cannot be definitively established. However, the panel recommends only intravenous pamidronate or zoledronic acid in light of the use of the time to first skeletal event as the primary end point and more complete assessment of bony complications in studies evaluating it. Additionally, clodronate is not available in the United States. The choice between pamidronate and zoledronic acid will depend on choosing between the higher drug cost of zoledronic acid, with its shorter, more convenient infusion time (15 minutes), versus the less expensive drug, pamidronate, with its longer infusion time (2 hours). CONCLUSION: **Bisphosphonates** provide a meaningful supportive benefit to multiple myeloma patients with lytic **bone disease**. However, further research on **bisphosphonates** is warranted, including the following: (1) when to start and stop therapy, (2) how to integrate their use with other treatments for lytic **bone disease**, (3) how to evaluate their role in myeloma patients without lytic bone involvement, (4) how to distinguish between symptomatic and asymptomatic bony events, and (5) how to better determine their cost-benefit consequence.

L33 ANSWER 4 OF 155 MEDLINE

ACCESSION NUMBER: 2001356152 MEDLINE
DOCUMENT NUMBER: 21311426 PubMed ID: 11417967
TITLE: Metastatic **bone disease**: clinical features, pathophysiology and treatment strategies.
AUTHOR: Coleman R E
CORPORATE SOURCE: Yorkshire Cancer Research Department of Clinical Oncology, Cancer Research Centre, Weston Park Hospital, Sheffield, U.K.
SOURCE: CANCER TREATMENT REVIEWS, (2001 Jun) 27 (3) 165-76. Ref: 53
Journal code: 7502030. ISSN: 0305-7372.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB Metastatic **bone disease** develops as a result of the many interactions between tumour cells and bone cells. This leads to disruption of normal bone metabolism, with the increased osteoclast activity seen in most, if not all, tumour types providing a rational target for treatment. The clinical course of metastatic **bone disease** in multiple myeloma, breast and prostate cancers is relatively long, with patients experiencing sequential skeletal complications over a period of several years. These include bone pain, fractures, hypercalcaemia and spinal cord compression, all of which may profoundly impair a patient's quality of life.External beam radiotherapy and systemic endocrine and cytotoxic treatments are the mainstay of treatment in advanced cancers. However, it is now clear that the **bisphosphonates** provide an additional treatment strategy, which reduces both the symptoms and complications of bone involvement. Ongoing research is aimed at trying to define the optimum route, dose, schedule and type of **bisphosphonate** in metastatic **bone disease** and in the **prevention** and treatment of osteoporosis in cancer patients. In vitro suggestions of direct anticancer activity and some promising clinical data in early breast cancer have resulted in considerable interest in the possible adjuvant use of **bisphosphonates** to inhibit the development of bone metastases.

L33 ANSWER 5 OF 155 MEDLINE
ACCESSION NUMBER: 90128940 MEDLINE
DOCUMENT NUMBER: 90128940 PubMed ID: 2137106
TITLE: Long-term effects of parenteral dichloromethylene **bisphosphonate** (CL2MBP) on **bone disease** of myeloma patients treated with chemotherapy.
AUTHOR: Merlini G; Parrinello G A; Piccinini L; Crema F; Fiorentini M L; Riccardi A; Pavesi F; Novazzi F; Silingardi V; Ascari E
CORPORATE SOURCE: Institute of Clinical Medicine II, University of Pavia, Italy.
SOURCE: HEMATOLOGICAL ONCOLOGY, (1990 Jan-Feb) 8 (1) 23-30. Journal code: 8307268. ISSN: 0278-0232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199003
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19900314

AB Data on the long-term treatment of myeloma **bone disease** with **bisphosphonates** are scanty. In a prospective pilot trial we evaluated the effect of long-term parenteral administration of dichloromethylene **bisphosphonate** (Clodronate), in addition to standard chemotherapy, in 30 patients with active myeloma **bone disease**. Patients were treated with a mean of 4 courses (range 2-8) of Clodronate: 300 mg/day i.v. for seven days followed by 100 mg/day i.m. for 10 days, administered at a mean interval of 4 months (range 3-6). The median follow-up was 24 months (range 8-36). Clodronate reduced bone

pain rapidly and significantly, and reduced the mean values of the biochemical indices of bone resorption to within normal limits; these effects were maintained throughout the follow-up. In three hypercalcemic episodes serum calcium became normal after 2-5 days of treatment with Clodronate. No toxic or side effects were noticed. The occurrence of skeletal morbidity in patients treated with Clodronate was compared with that observed in the control group of myeloma patients (p less than 0.001) in severe bone pain as well as in the incidence of new osteolytic lesions and pathological fractures (p less than 0.001). Supportive Clodronate therapy contributes significantly in controlling the progression of myeloma **bone disease**.

L33 ANSWER 6 OF 155 MEDLINE
ACCESSION NUMBER: 2001237302 MEDLINE
DOCUMENT NUMBER: 21197997 PubMed ID: 11301184
TITLE: Ibandronate decreases **bone disease** development and osteoclast stimulatory activity in an in vivo model of human myeloma.
AUTHOR: Cruz J C; Alsina M; Craig F; Yoneda T; Anderson J L; Dallas M; Roodman G D
CORPORATE SOURCE: Department of Medicine, Texas Tech University, Lubbock, TX, USA.
CONTRACT NUMBER: CA40035 (NCI)
CA69136 (NCI)
SOURCE: EXPERIMENTAL HEMATOLOGY, (2001 Apr) 29 (4) 441-7.
Journal code: 0402313. ISSN: 0301-472X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010503

AB The benefits of **bisphosphonate** therapy for multiple myeloma **bone disease** have been clearly documented. However, the effects of **bisphosphonates** on the osteoclast stimulatory activity (OSA) that is present in the marrow of patients with multiple myeloma, even before the **bone disease** is detectable, are unknown. Therefore, we examined the effects of ibandronate (IB) treatment prior to the development of **bone disease** in a murine model of human myeloma.Sublethally irradiated severe combined immunodeficient (SCID) mice were transplanted with ARH-77 cells on day 0. These ARH-77 mice were treated daily with subcutaneous injections of IB started before or at different times after tumor injection as follows: group 1 was started on day -7; group 2 on day 0; group 3 on day +7; group 4 on day +14 after IB administration; and group 5 (control) received no IB. Mice were sacrificed after they developed paraplegia.The onset of paraplegia was delayed in group 1 vs all other groups (mean day 27 vs day 32; p = 0.0098). The number of lytic lesions and the bone surface area of resorption (mm(2)) were significantly decreased in groups 1, 2, and 3, which were treated early with IB, when compared with groups 4 and 5 (p = 0.003 and 0.002, respectively). OSA, as measured by the capacity of bone marrow plasma from ARH-77 mice to induce osteoclast (OCL) formation in human bone marrow cultures, was decreased proportionally to the length of IB treatment. Group 1 had the lowest OSA compared with the other groups (p = 0.003). However, all mice eventually developed paraplegia, and at time of sacrifice, tumor burden was not grossly different among the groups. Interestingly, macroscopic abdominal tumors were more frequent in mice treated with IB.These data demonstrate that early treatment of ARH-77 mice with IB prior to development of myeloma **bone disease** decreases OSA and possibly retards the development of

lytic lesions, but not eventual tumor burden.

L33 ANSWER 7 OF 155 MEDLINE
ACCESSION NUMBER: 2002123523 MEDLINE
DOCUMENT NUMBER: 21847146 PubMed ID: 11858352
TITLE: **Bisphosphonates** in **bone diseases** other than osteoporosis.
COMMENT: Comment in: Joint Bone Spine. 2002 Oct;69(5):521; author reply 522
AUTHOR: Orcel Philippe; Beaudreuil Johann
CORPORATE SOURCE: Federation de rhumatologie, centre Viggo-Petersen, hjpital Lariboisiere, Paris, France.. philippe.orcel@lrb.ap-hop-paris.fr
SOURCE: JOINT, BONE, SPINE, (2002 Jan) 69 (1) 19-27. Ref: 68
Journal code: 100938016. ISSN: 1297-319X.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020223
Last Updated on STN: 20020808
Entered Medline: 20020807

AB The range of **bone diseases** in which **bisphosphonates** are used has extended far beyond osteoporosis during the last few years. **Bisphosphonate** therapy is now so well validated as to be the reference standard in Paget's disease and in the **prevention** of bone complications related to malignant osteolysis. Promising preliminary findings warrant the use of **bisphosphonates** in conditions that are either rare (fibrous dysplasia) or severe (pediatric osteogenesis imperfecta). The third category of indications encompasses many conditions in which the limited available data do not warrant widespread use: examples include reflex sympathetic dystrophy syndrome, acute back pain after a vertebral crush fracture, and chronic inflammatory joint disease not treated by glucocorticoids.

L33 ANSWER 8 OF 155 MEDLINE
ACCESSION NUMBER: 2003039315 MEDLINE
DOCUMENT NUMBER: 22434863 PubMed ID: 12548581
TITLE: **Bisphosphonates** and osteoprotegerin as inhibitors of myeloma **bone disease**.
AUTHOR: Croucher Peter I; Shipman Claire M; Van Camp Ben; Vanderkerken Karin
CORPORATE SOURCE: Nuffield Department of Orthopaedic Surgery, University of Oxford, Nuffield Orthopaedic Centre, Oxford, United Kingdom.. peter.croucher@ndos.ox.ac.uk
SOURCE: CANCER, (2003 Feb 1) 97 (3 Suppl) 818-24.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030128
Last Updated on STN: 20030416
Entered Medline: 20030414

AB BACKGROUND: A major clinical feature in multiple myeloma is the development of osteolytic **bone disease**. The increase in bone destruction is due to uncontrolled osteoclastic bone resorption.

Until recently the factors responsible for mediating the increase in osteoclast formation in myeloma have been unclear. However, recent studies have implicated a number of factors, including the ligand for receptor activator of NFkappaB (RANKL) and macrophage inflammatory protein-1alpha. The demonstration that increased osteoclastic activity plays a central role in this process and the identification of molecules that may play a critical role in the development of myeloma **bone disease** have resulted in studies aimed at identifying new approaches to treating this aspect of myeloma. METHODS: Studies have been performed to determine the ability of recombinant osteoprotegerin (Fc.OPG), a soluble decoy receptor for RANKL, and potent new **bisphosphonates** to inhibit the development of myeloma **bone disease** in the 5T2MM murine model of multiple myeloma. RESULTS: Fc.OPG was shown to prevent the development of osteolytic bone lesions in 5T2MM bearing animals. These changes were associated with a preservation of the cancellous bone loss induced by myeloma cells and an inhibition of osteoclast formation. **Bisphosphonates**, including ibandronate and zoledronic acid, were also shown to inhibit the development of osteolytic bone lesions in the 5T2MM model and alternative models of myeloma **bone disease**. CONCLUSIONS: **Bisphosphonates** and Fc.OPG are effective inhibitors of the development of osteolytic bone lesions in pre-clinical murine models of myeloma **bone disease**.
DOI 10.1002/cncr.11125

L33 ANSWER 9 OF 155 MEDLINE
ACCESSION NUMBER: 2001259809 MEDLINE
DOCUMENT NUMBER: 21063123 PubMed ID: 11114866
TITLE: Optimising treatment of bone metastases by Aredia(TM) and Zometa(TM).
AUTHOR: Coleman R E
CORPORATE SOURCE: Department of Clinical Oncology, Cancer Research Centre, Weston Park Hospital, Whitham Road, Sheffield, S10 2SJ, UK.
SOURCE: BREAST CANCER, (2000) 7 (4) 361-9.
Journal code: 100888201. ISSN: 1340-6868.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB Metastatic **bone disease** develops as a result of the many interactions between tumour cells and bone cells. This leads to disruption of normal bone metabolism, with the increased osteoclast activity seen in most, if not all, tumor types providing a rational target for treatment. The clinical course of metastatic **bone disease** in multiple myeloma, breast and prostate cancers is relatively long, with patients experiencing sequential skeletal complications over a period of several years. These include bone pain, fractures, hypercalcaemia, and spinal cord compression, all of which may profoundly impair a patient's quality of life. External beam radiotherapy and systemic endocrine and cytotoxic treatments are the mainstay of treatment in advanced cancers. However, it is now clear that the **bisphosphonates** provide an additional treatment strategy, which reduces both the symptoms and complications of bone involvement. Pamidronate (Aredia(TM)) is the most widely evaluated **bisphosphonate** and is recommended for most patients with multiple myeloma or breast cancer with bone metastases. Current research aims include the evaluation of new potent **bisphosphonates** such as zoledronic acid (Zometa(TM)). It is hoped that this compound is not only

more convenient and easier to administer but also more effective in inhibiting skeletal morbidity. Zometa may also have some direct anticancer activity. Preclinical studies with Zometa have demonstrated its potential in malignant **bone disease**. Clinical studies in treatment of hypercalcemia of malignancy have been completed, as have Phase I and II trials in patients with cancer and pre-existing bone metastases. Three randomized, double-blind, controlled Phase III trials are now ongoing to establish the efficacy and safety of Zometa in treatment of bone metastases in patients with osteolytic and osteoblastic lesions. Additionally, new specific molecules such as osteoprotogerin have been developed that are based on our improved understanding of the cellular signalling mechanisms involved in cancer induced **bone disease**. These potent molecules are now entering clinical trials. Ongoing research is aimed at trying to define the optimum route, dose, schedule and type of **bisphosphonate** in metastatic **bone disease** and their use in the **prevention** and treatment of osteoporosis in cancer patients. In vitro suggestions of direct anti-cancer activity and some promising clinical data in early breast cancer have resulted in considerable interest in the possible adjuvant use of **bisphosphonates** to inhibit the development of bone metastases.

L33 ANSWER 10 OF 155 MEDLINE
ACCESSION NUMBER: 97027500 MEDLINE
DOCUMENT NUMBER: 97027500 PubMed ID: 8873639
TITLE: Clinical practice guidelines for the diagnosis and management of osteoporosis. Scientific Advisory Board, Osteoporosis Society of Canada.
AUTHOR: Anonymous
SOURCE: CMAJ, (1996 Oct 15) 155 (8) 1113-33.
Journal code: 9711805. ISSN: 0820-3946.
PUB. COUNTRY: Canada
DOCUMENT TYPE: (GUIDELINE)
Journal; Article; (JOURNAL ARTICLE)
(PRACTICE GUIDELINE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19980206
Entered Medline: 19961112

AB OBJECTIVE: To recommend clinical practice guidelines for the assessment of people at risk for osteoporosis, and for effective diagnosis and management of the condition. OPTIONS: Screening and diagnostic methods: risk-factor assessment, clinical evaluation, measurement of bone mineral density, laboratory investigations. Prophylactic and corrective therapies: calcium and vitamin D nutritional supplementation, physical activity and fall-avoidance techniques, ovarian hormone therapy, **bisphosphonate** drugs, other drug therapies. Pain-management medications and techniques. OUTCOMES: **Prevention** of **loss** of **bone mineral** density and fracture; increased bone mass; and improved quality of life. EVIDENCE: Epidemiologic and clinical studies and reports were examined, with emphasis on recent randomized controlled trials. Clinical practice in Canada and elsewhere was surveyed. Availability of treatment products and diagnostic equipment in Canada was considered. VALUES: Cost-effective methods and products that can be adopted across Canada were considered. A high value was given to accurate assessment of fracture risk and osteoporosis, and to increasing bone mineral density, reducing fractures and fracture risk and minimizing side effects of diagnosis and treatment. BENEFITS, HARMS AND COSTS: Proper diagnosis and management of osteoporosis minimize injury and disability, improve quality of life for patients and

reduce costs to society. Rationally targeted methods of screening and diagnosis are safe and cost effective. Harmful side effects and costs of recommended therapies are minimal compared with the harms and costs of untreated osteoporosis. Alternative therapies provide a range of choices for physicians and patients. RECOMMENDATIONS: Population sets at high risk should be identified and then the diagnosis confirmed through bone densitometry. Dual-energy x-ray absorptiometry is the preferred measurement technique. Radiography can be adjunct when indicated. Calcium and vitamin D nutritional supplementation should be at currently recommended levels. Patients should be counselled in fall-avoidance techniques and exercises. Immobilization should be avoided. Guidelines for management of acute pain are listed. Ovarian hormone therapy is the therapy of choice for osteoporosis **prevention** and treatment in postmenopausal women. **Bisphosphonates** are an alternative therapy for women with established osteoporosis who cannot or prefer not to take ovarian hormone therapy.

L33 ANSWER 11 OF 155 MEDLINE
ACCESSION NUMBER: 96434620 MEDLINE
DOCUMENT NUMBER: 96434620 PubMed ID: 8837544
TITLE: **Prevention** and management of osteoporosis: consensus statements from the Scientific Advisory Board of the Osteoporosis Society of Canada. 6. Use of **bisphosphonates** in the treatment of osteoporosis.
AUTHOR: Hodsman A; Adachi J; Olszynski W
CORPORATE SOURCE: Department of Medicine, University of Western Ontario, St. Joseph's Health Centre, London.
SOURCE: CMAJ, (1996 Oct 1) 155 (7) 945-8. Ref: 34
Journal code: 9711805. ISSN: 0820-3946.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Conference; (CONSENSUS DEVELOPMENT CONFERENCE)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19980206
Entered Medline: 19961107

AB OBJECTIVE: To describe the mechanisms of action of **bisphosphonates** in the treatment of osteoporosis and compare **bisphosphonate** therapy with other treatments. OPTIONS: The **bisphosphonates**, etidronate, alendronate, clodronate, pamidronate, tiludronate, ibandronate and risedronate; combined **bisphosphonates** and estrogen; combined **bisphosphonates** and calcium supplements. OUTCOMES: Fracture and **loss** of **bone mineral** density in osteoporosis; increased bone mass, **prevention** of fractures and improved quality of life associated with **bisphosphonate** treatment. EVIDENCE: Relevant clinical studies and reports were examined with emphasis on recent controlled trials. The availability of treatment products in Canada was also considered. VALUES: Reducing fractures, increasing bone mineral density and minimizing side effects of treatment were given a high value. BENEFITS, HARMS AND COSTS: Treatment with **bisphosphonates** may be an acceptable alternative to ovarian hormone therapy in increasing bone mass and decreasing fractures associated with osteoporosis. Compared with estrogens, **bisphosphonates** are bone-tissue specific, have equal or greater antiresorptive effect and have few side effects and no known risk for carcinogenesis. They also hold promise in treating male osteoporosis and steroid-induced bone loss. Prolonged, continuous treatment with etidronate may lead to impaired calcification of newly formed bone; therefore, etidronate is administered cyclically. This risk is not